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## Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer (Review)

Lawrie TA, Winter-Roach BA, Heus P, Kitchener HC

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[Intervention Review]

# Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer

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## ABSTRACT

### Background

This is the second update of the review first published in the Cochrane Database of Systematic Reviews in 2009, Issue 1. Epithelial ovarian cancer is diagnosed in over 200,000 women worldwide each year. Ten to 20% of women are diagnosed early, when there is still a good possibility of cure. The treatment of early-stage (stage I and IIa) disease involves surgery to remove the disease, often followed by chemotherapy (adjuvant chemotherapy). The largest clinical trials of adjuvant chemotherapy show an overall survival (OS) advantage with platinum-based chemotherapy; however the precise role and type of this treatment in subgroups of women with differing prognoses needs to be defined.

### Objectives

To undertake a systematic review of the evidence for adjuvant chemotherapy in early-stage epithelial ovarian cancer to determine whether chemotherapy following surgery offers a survival advantage over the policy of observation following surgery (with chemotherapy reserved for treatment of disease recurrence); and to determine if clinical subgroups of women with differing prognoses, based on histological subtype or completeness of surgical staging, have more or less to gain from adjuvant chemotherapy.

### Search methods

We performed an electronic search using the Cochrane Gynaecological Cancer Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 3), MEDLINE (1948 to March week 5, 2015), and EMBASE (1980 to week 14, 2015). We developed the search strategy using free-text and medical subject headings (MeSH). We also searched registers of clinical trials and citation lists of included studies for potentially relevant studies.

### Selection criteria

We included randomised clinical trials (RCTs) of women with early stage (I/IIa) epithelial ovarian cancer staged at laparotomy.

### Data collection and analysis

Two review authors independently extracted data and assessed study quality of included RCTs. We resolved any disagreements by discussion with a third review author. We used random-effects methods for all meta-analyses, including subgroup analyses.

## Main results

The original version of this Cochrane review included five RCTs involving 1277 women. In this 2015 update, no new studies met the inclusion criteria but we included an additional paper with mature data (10-year follow-up) relating to a previously included study (ICON1).

We included four studies in the meta-analyses and considered them to be at a low risk of bias. Most study participants (> 95%) had stage I ovarian cancer. Meta-analysis of five-year data from three studies indicated that women who received adjuvant platinum-based chemotherapy had better overall survival (OS) than those who did not (Hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.53 to 0.93; 1008 women; 3 studies;  $I^2$  statistic = 0%; *high quality evidence*). Likewise, meta-analysis of five-year data from four studies indicated that women who received adjuvant chemotherapy had better progression-free survival (PFS) than those who did not (HR 0.67, 95% CI 0.53 to 0.84; 1170 women, 4 studies;  $I^2$  statistic = 0%; *high quality evidence*). These findings were robust over time, with 10-year HR estimates of 0.72 (95% CI 0.57 to 0.92; 925 women, 2 studies) and 0.67 (95% CI 0.53 to 0.83; 925 women, 2 studies) for OS and PFS, respectively (*high quality evidence*). The risk of death at 10 years follow-up favoured the adjuvant chemotherapy arm (0.76, 95% CI 0.62 to 0.94; 923 women, 2 studies;  $I^2$  statistic = 0%), as did the findings for risk of progression at 10 years (RR 0.72, 95% CI 0.60 to 0.87; 925 women, 2 studies;  $I^2$  statistic = 0%). Low quality evidence suggested that women with high-risk disease may have the most to gain from adjuvant chemotherapy. However, subgroup analyses could neither confirm nor exclude survival benefits in lower risk disease or in optimally staged disease. We found insufficient data to compare adverse events and long term risks between chemotherapy and observation groups.

## Authors' conclusions

High-quality evidence indicates that adjuvant platinum-based chemotherapy is effective in prolonging survival in women with early stage (FIGO stage I/IIa) epithelial ovarian cancer. It remains uncertain whether women with low- and intermediate-risk early stage disease will benefit as much from adjuvant chemotherapy as women with high-risk disease. Decisions to use adjuvant chemotherapy (AC) in these women should be mindful of this uncertainty, and the uncertainty regarding adverse events. Treatment of women with lower risk disease should be individualised to take into account individual factors.

## PLAIN LANGUAGE SUMMARY

### Post-surgery (adjuvant) chemotherapy for early stage epithelial ovarian cancer

#### What is the issue?

The initial treatment of ovarian cancer (OC) is surgery to remove the cancerous tissue. This also serves to stage the disease. Staging surgery in OC is considered optimal (complete) when it includes removal of the womb, fallopian tubes, and ovaries, as well as removal of the fatty apron attached to the gut (omentum), and sampling of the abdominal fluid, pelvic and para-aortic lymph nodes, the side walls of the pelvis and paracolic gutters, and the diaphragm. OC is also graded 1, 2, or 3 (well-, moderately-, or poorly-differentiated), with well-differentiated (grade 1) OC associated with the best prognosis. After surgery, most women with OC are offered adjuvant (added) chemotherapy with platinum-containing drugs. However, in the past women with stage Ia and Ib have not routinely been offered chemotherapy because the risk of treatment complications may outweigh the survival benefits.

This is an update of a previous version of this Cochrane review, which found that women with early-stage OC who received adjuvant chemotherapy (AC) lived longer than women who did not, and took longer for their disease to recur after initial treatment.

#### What did we do?

We included randomised controlled trials (RCTs) of AC versus observation after surgery in women diagnosed with early-stage OC and pooled study outcome data where appropriate.

#### What evidence did we find?

We searched the literature up to 24th March 2015 and included five trials involving 1277 women with early-stage OC in the review, and four good quality trials contributed data. Most women (more than 95%) had stage I OC. For this update, we identified one additional publication of 10-year follow-up results from a trial already included in the review, but found no new trials. We found high quality evidence that women diagnosed with early-stage OC who received AC after surgery to remove and stage the disease had a lower risk of dying within 10 years than women who did not receive AC (observation group), and a lower risk of the cancer returning in the 10 years after treatment (see Cates plot, Figures 4 to 7). Low quality evidence suggested that women with higher risk disease may have more to gain from AC, but we could not exclude a survival benefit for other early stage disease. Chemotherapy can have side effects but we found insufficient data to compare adverse events and long term risks between chemotherapy and observation groups.

#### What does this mean?

In early stage ovarian cancer, AC improves survival and reduces the risk of ovarian cancer recurring compared with no AC. Therefore AC in early stage disease should be considered in all women. However, it remains uncertain whether women with lower risk early stage disease will benefit much from AC and decisions to use AC should be mindful of this uncertainty, and the uncertainty regarding adverse events.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Summary of main findings

#### Adjuvant chemotherapy compared with observation for early stage ovarian cancer (primary review outcomes)

**Patient or population:** women with stage I/II epithelial ovarian cancer

**Settings:** hospital and outpatient

**Intervention:** chemotherapy following surgery

**Comparison:** observation following surgery

Outcomes	Illustrative comparative risks		HR (95% CI)  Chemotherapy versus obser- vation	Number of par- ticipants ( studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk (Observation)	Corresponding risk (Chemotherapy)				
<b>Overall 5-year survival<sup>1</sup></b>	22 deaths out of 100 women	16 out of 100 women (12 to 20)	<b>HR 0.71</b> (0.53 to 0.93)	1008 women (three studies)	⊕⊕⊕⊕ <b>high</b>	I <sup>2</sup> statistic = 0%  P = 0.01  HR < 1 indicates a clinical advantage for adjuvant chemotherapy
<b>Progres- sion-free 5- year survival<sup>2</sup></b>	32 women with pro- gressive disease out of 100 women	22 women with progres- sive disease out of 100 women (18 to 27)	<b>HR 0.67</b> (0.53 to 0.84)	1170 women (four studies)	⊕⊕⊕⊕ <b>high</b>	I <sup>2</sup> statistic = 0%  P = 0.0005  HR < 1 indicates a clinical advantage for adjuvant chemotherapy
<b>Overall 10- year<sup>3</sup> survival</b>	33 deaths out of 100 women	25 deaths out of 100 women (20 to 31)	<b>HR 0.72</b> (0.57 to 0.92)	925 women (two studies)	⊕⊕⊕⊕ <b>high</b>	I <sup>2</sup> statistic = 0%  P = 0.007  HR < 1 indicates a clinical advantage for adjuvant chemotherapy
<b>Progres- sion-free 10- year survival<sup>4</sup></b>	39 women with pro- gressive disease out of 100 women	28 women with progres- sive disease out of 100 women (23 to 34)	<b>HR 0.67</b> (0.53 to 0.83)	925 women (two studies)	⊕⊕⊕⊕ <b>high</b>	I <sup>2</sup> statistic = 0%  P = 0.0004

HR < 1 indicates a clinical advantage for adjuvant chemotherapy

**Adverse events** Not estimable. Trials did not report comparative rates of adverse events.

**Abbreviations; CI:** confidence interval; **HR:** hazard ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>The illustrative assumed and corresponding 5-year risks were based on the RR (dichotomous data) from [Analysis 1.2](#) (RR 0.72, 95% CI 0.56 to 0.93; 1089 participants; 4 studies; I<sup>2</sup> statistic = 0%), where the assumed risk was the mean observation group risk.

<sup>2</sup>The illustrative assumed and corresponding 5-year risks were based on the RR (dichotomous data) from [Analysis 1.6](#) (RR 0.69, 95% CI 0.57 to 0.84; 1089 participants; 4 studies; I<sup>2</sup> statistic = 0%), where the assumed risk was the mean observation group risk.

<sup>3</sup>The illustrative assumed and corresponding 10-year risks were based on the RR (dichotomous data) from [Analysis 1.4](#) (RR 0.76, 95% CI 0.62 to 0.94; 923 participants; 2 studies), where the assumed risk was the mean observation group risk.

<sup>4</sup>The illustrative assumed and corresponding 10-year risks were based on the RR (dichotomous data) from [Analysis 1.8](#) (RR 0.72, 95% CI 0.60 to 0.87; 925 participants; 2 studies), where the assumed risk was the mean observation group risk.

## BACKGROUND

### Description of the condition

This is an updated version of the Cochrane review first published in the Cochrane Database of Systematic Reviews in 2009 ([Winter-Roach 2009](#)) and updated in 2012 ([Winter-Roach 2012](#)). Ovarian cancer is the seventh most common cancer among women up to 64 years of age. Worldwide there are more than 200,000 new cases of ovarian cancer each year, accounting for around 4% of all cancers diagnosed in women and giving a cumulative lifetime risk of ovarian cancer of 0.5% ([GLOBOCAN 2012](#)). In Europe, ovarian cancer is the leading cause of gynaecological cancer death, with just over a third of women alive five years after diagnosis ([Sant 2003](#)). Ovarian cancer is associated with high mortality rates because most women are diagnosed when the cancer is already at an advanced stage and surgical cure is impossible ([Jemal 2008](#)).

Over 85% of ovarian cancers develop in the surface (epithelial) cells of the ovary. There are different types based on microscopic features (histopathological types) of which the most common are serous. Endometrioid, mucinous, and clear cell cancers are less common and the malignant Brenner type is rare. Malignant tumours are characterised by their grade; this describes the microscopic pattern of growth (architecture) and cellular features (cytology) and varies from well differentiated (grade G1) to moderately and poorly differentiated (G2 and G3 respectively). Well-differentiated tumours are of better prognosis than G2 or G3 tumours. FIGO staging is used to describe the spread of the disease. FIGO stage I disease is confined to one or both ovaries and FIGO stage II disease is limited in spread to the true pelvis. FIGO stage I is subdivided into three stages, Ia to Ic. In stage Ia, the disease is confined to one ovary with no involvement of the ovarian surface and with no tumour cells in the fluid of the abdominal cavity (negative peritoneal washings); stage Ib indicates similarly encapsulated disease in both ovaries but with no evidence of other spread; and stage Ic indicates ovarian cyst rupture or ascites containing malignant cells ([Shepherd 1989](#)). FIGO stage II was similarly divided into three substages but stage IIc was abolished in 2014. Stage IIa indicates spread to the uterus or fallopian tubes; and stage IIb indicates spread to other pelvic structures (see [Table 1](#) for full details of FIGO staging). Less than 30% of women present with stage I or II ovarian cancer ([Jemal 2008](#)).

Women with early ovarian cancer should be offered surgery, both to remove the disease and to provide accurate staging, which is a key factor in assessing the impact of different treatments in this patient group. The pattern of spread of ovarian cancer is such that small deposits of tumour 'hidden' in the upper abdomen and retro-peritoneum can be readily missed. It has been shown that a significant percentage of women will be understaged if the initial staging surgery is suboptimal. If upper abdominal disease is missed, a woman with apparent stage Ic disease may actually have stage III disease. Currently there is a lack of accurate molecular or imaging markers to predict prognosis and identify women with occult disease. Accurate staging helps provide better prediction of outcome in individual cases, is an independent prognostic factor for survival in stage I disease ([Trimbos 2003](#); [Zanetta 1998](#)), and influences ongoing management.

Recent reports have confirmed a very good prognosis for women with stage Ia disease treated with conservation of the contralateral ovary in order to preserve their fertility ([Morice 2001](#); [Schilder 2002](#)).

A proportion of patients with stage I disease will be cured by their surgery and it may be that the chance of survival is improved if the surgery is undertaken by a trained gynaecological oncologist ([Mayer 1992](#)). There is evidence from a randomised controlled trial (RCT) that systematic pelvic and para-aortic lymphadenectomy will identify more women with lymph node metastases than sampling of suspicious nodes ([Maggioni 2006](#)); no survival difference was seen in this trial although it was underpowered to examine this outcome. There is, however, a high incidence of recurrent disease, which can be as high as 30% in certain subgroups of women with stage I disease. The challenge is to determine which patients are at high risk and would benefit most from additional treatment.

Uncontrolled retrospective studies have identified prognostic factors of importance for this disease. A multivariate analysis of 1545 patients with stage I epithelial ovarian cancer confirmed tumour grade to be the single most important determinant of survival ([Vergote 2001](#)). In addition, capsular involvement or cyst rupture (FIGO stage Ic) were associated with a poorer outcome. The current staging for ovarian cancer does not recognise the prognostic importance of tumour grade.

Another issue relates to the class of ovarian cancers of low malignant potential known as borderline tumours. These neoplasms tend to run a benign course; however adverse prognostic factors are similarly based on histological features. These concerns have prompted calls for a revision of FIGO staging to incorporate the borderline tumours and endorse the importance of tumour grade ([Green 2003](#)).

### Description of the intervention

Adjuvant treatment is any treatment given after surgical removal of all visible disease in order to reduce the risk of recurrence. Given the significant risk of recurrence in subgroups of patients with completely resected early stage disease, adjuvant treatment is usually considered. The rationale for this treatment is to eradicate any microscopic deposits of tumour that may remain after surgery. Several underpowered clinical trials have examined the merits of adjuvant chemotherapy compared with adjuvant radiotherapy in selected subgroups ([Chiara 1994](#); [Hreshchyshyn 1980](#); [Klaassen 1988](#); [Sigurdsson 1982](#)).

A Cochrane review and meta-analysis of individual patient data ([AOCTG 1999](#)) confirmed modest two- and five-year survival advantages in women with advanced stage epithelial ovarian cancer who were given platinum-based combination chemotherapy compared with those given combination therapy lacking platinum (hazard ratio (HR) 0.88, 95% confidence interval (CI) 0.79 to 0.98; [AOCTG 1999](#)). [ICON2 1998](#) subsequently confirmed equivalent efficacy (and lower toxicity) of single-agent carboplatin compared with a combination regimen of cyclophosphamide, doxorubicin, and cisplatin (CAP) and recommended it as the standard initial treatment of advanced stage epithelial ovarian cancer. [GOG111 1996](#) demonstrated that survival was improved by adding paclitaxel to first-line platinum-based chemotherapy. Hence, the recommended first-line chemotherapy for advanced epithelial ovarian cancer is a platinum agent combined with a taxane. Furthermore, the Gynecologic Cancer InterGroup continues to recommend carboplatin and paclitaxel as the standard comparator arm for trials in ovarian cancer treatment ([Thigpen 2011](#)).

Based on the results seen in advanced disease, platinum-based chemotherapy has been adopted for use in early stage disease. Accepted practice in the UK is to offer six cycles of adjuvant chemotherapy (with or without a taxane) to women with stage Ic disease or more. With regard to low-risk disease, the NICE 2011 clinical guideline on ovarian cancer states that adjuvant chemotherapy should not be offered to women with low-risk stage I disease (grade 1 or 2, stage Ia or Ib) if they have undergone optimal staging, and should be discussed with women who have had suboptimal staging (NICE 2011).

### Why it is important to do this review

Various systematic reviews of adjuvant therapy including radiotherapy in early-stage epithelial ovarian cancer have been published (Elit 2004; Tropé 2007; New Reference). Most agree that stage Ia grade 1 disease does not need adjuvant chemotherapy; however, there is confusion over the best management of other early stage tumours as the risks of treatment complications may outweigh the survival benefits. Therefore, the precise role of chemotherapy in stage I disease continues to be the subject of some discussion. Clarity is needed on the subgroups of women, if any, that can safely be managed without adjuvant chemotherapy, and whether particular groups of women have more to gain from it. This updated Cochrane review aims to collate all the relevant data in the area, including long-term data from previously reviewed trials, to determine the overall benefit of adjuvant chemotherapy in women with early stage epithelial ovarian cancer and to give further guidance on which women should be offered chemotherapy.

## OBJECTIVES

### Primary objective

To assess the efficacy of adjuvant chemotherapy in early stage ovarian cancer in terms of overall survival (OS) and progression-free survival (PFS).

### Secondary objectives

To determine if there are some patients with early stage disease who are more or less likely to benefit from this treatment (i.e. optimal versus suboptimal staging, low risk versus high risk).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs).

#### Types of participants

Women with early stage (I/IIa) epithelial ovarian cancer staged at laparotomy.

#### Types of interventions

Adjuvant chemotherapy versus no adjuvant chemotherapy or placebo.

We defined the term adjuvant as treatment given within three months following surgery which removed all visible disease.

#### Types of outcome measures

##### Primary outcomes

- Overall survival (OS) (survival until death from any cause);
- Progression-free survival (PFS) or recurrence-free survival (RFS) (for the purposes of this Cochrane review, we have considered PFS and RFS to be the same endpoint).

##### Secondary outcomes

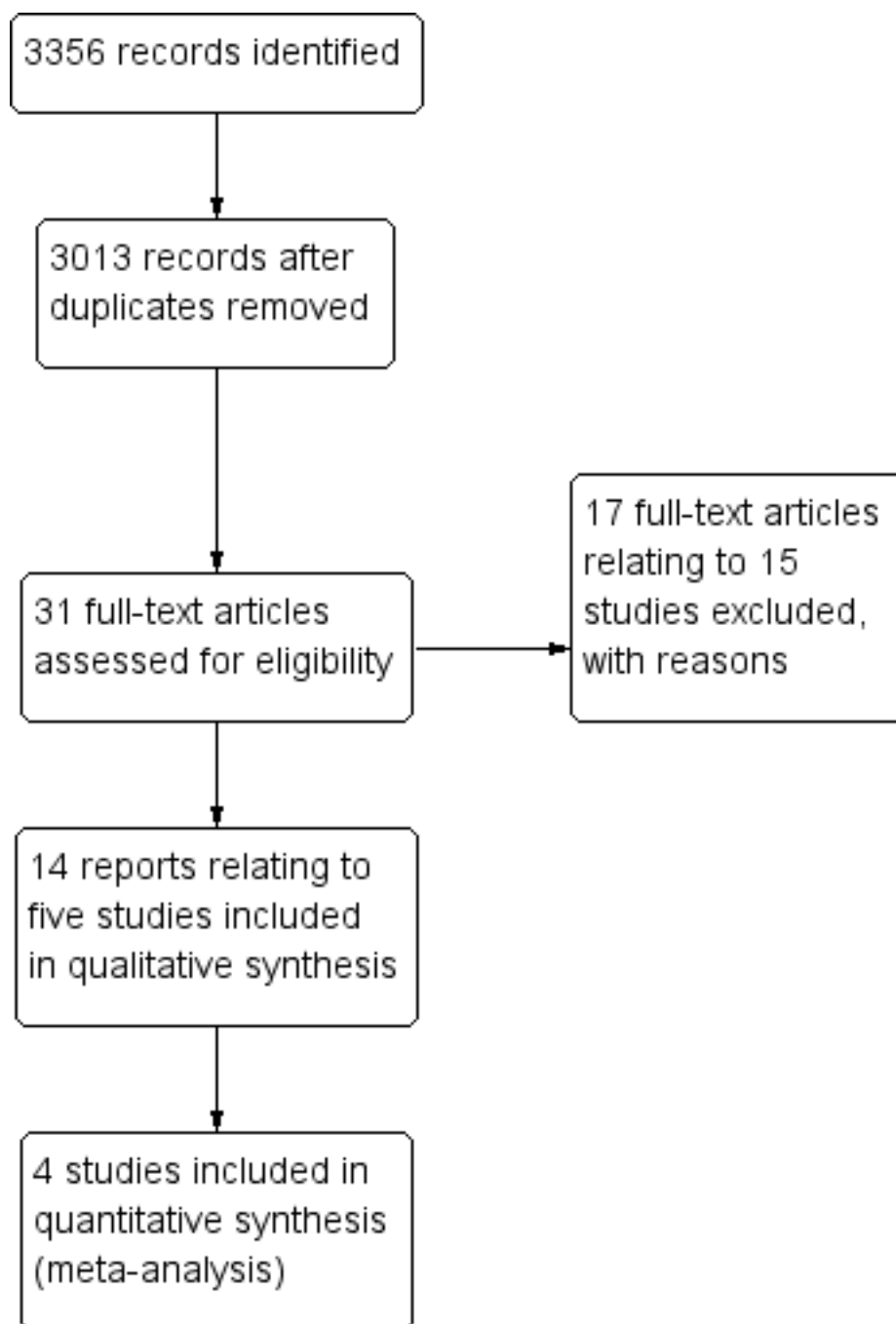
- Disease-specific survival (DSS) (defined as survival until death from ovarian cancer or complications of treatment, with deaths from other causes censored);
- Adverse events, extracted and grouped as:
  - haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage)
  - gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis)
  - genitourinary
  - skin (stomatitis, mucositis, alopecia, allergy)
  - neurological (peripheral and central)
  - pulmonary.

### Search methods for identification of studies

#### Electronic searches

For the original review (Winter-Roach 2009) and update (Winter-Roach 2012), we performed electronic searches up to August 2011 using the Cochrane Gynaecological Cancer Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL 2011, Issue 3) (Appendix 1), MEDLINE (1948 to Aug week 5, 2011) (Appendix 2) and EMBASE (1980 to week 36, 2011) (Appendix 3). This yielded a large number of article titles which two review authors (BW, HK and/or TL) screened and we independently reviewed the full-text versions of potentially relevant articles to the review question (see Figure 1 for search flow diagram). We handsearched the clinical literature, where appropriate, to identify additional full-text papers or abstracts of other directly relevant clinical trials. We applied no language restrictions.

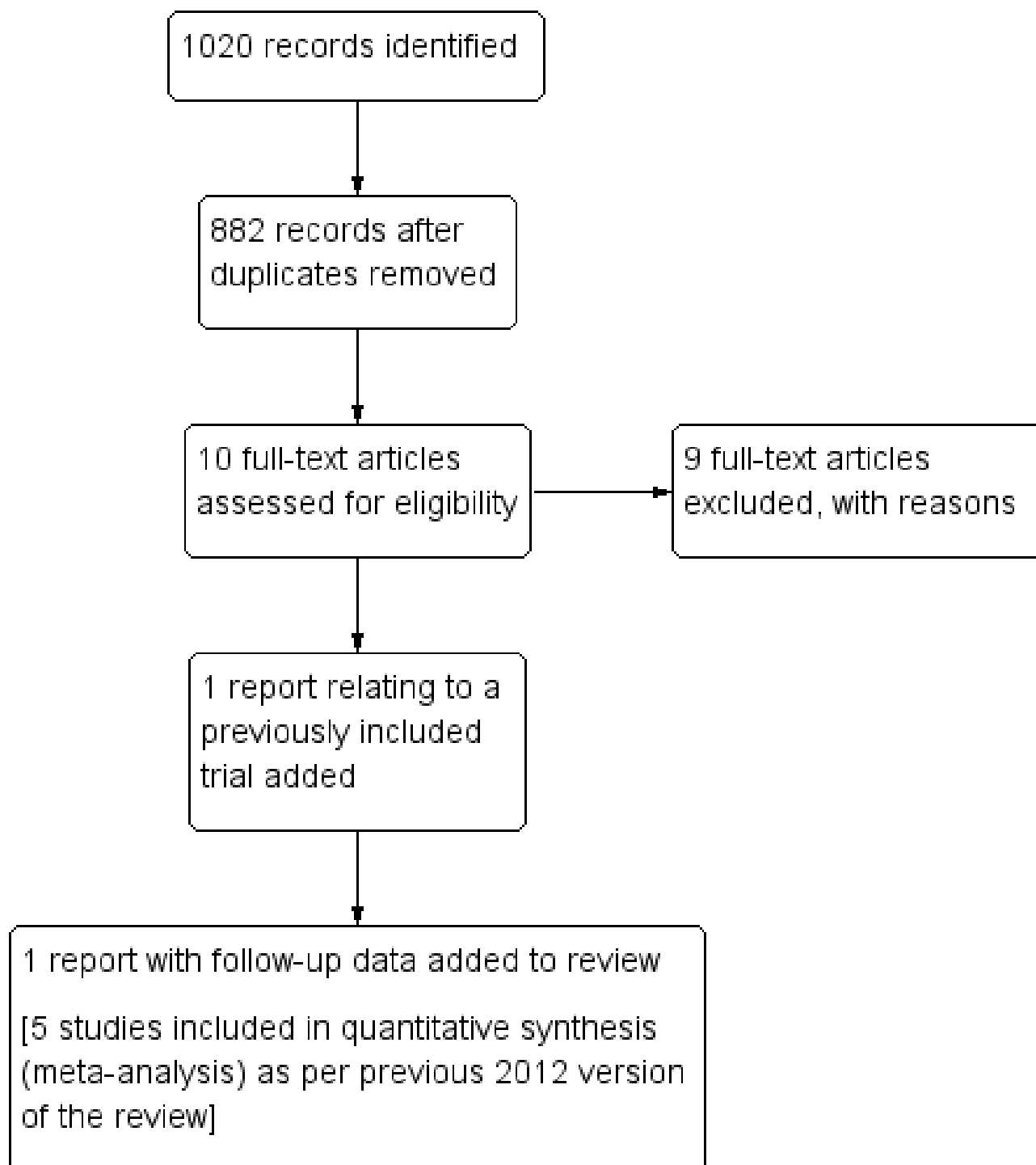
**Figure 1. Study flow diagram of search results (up to August 2011).**



For this 2015 update, the Information Manager of the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group, performed the literature searches on the 24 March 2015 to include the Cochrane Gynaecological Cancer Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL; Issue 2, 2015), MEDLINE (up to March week 5 2015), and EMBASE (up to

2015 week 14). In total, we identified 1020 potentially relevant references; 882 references after removal of duplicates. PH and LH excluded 872 records based on title and abstract, and excluded nine of the remaining 10 references after full-text screening (Figure 2). We included one paper, [Collinson 2014](#), which was a 10-year follow-up report of a previously included trial ([ICON1 2003](#)).

**Figure 2. Study flow diagram of the literature search results (24 March 2015).**



#### Searching other resources

We searched the bibliographies of all relevant papers selected through this strategy. We identified relevant articles on PubMed, and using the 'related articles' feature, we carried out a further search for newly published articles. In addition, we searched MetaRegister (<http://www.controlled-trials.com/mrct>), Physicians Data Query (<http://www.nci.nih.gov>), <http://www.clinicaltrials.gov>, and <http://www.cancer.gov/clinicaltrials/search> for ongoing trials.

We established personal communication with corresponding study authors and clinical experts where possible to enquire about other published or unpublished relevant studies.

#### Data collection and analysis

##### Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database and removed

duplicates. Two review authors (BWR and HK) independently examined the remaining references. For the 2011 search update, TL performed this task. For the 2015 search update, PH and LH conducted this task. We included studies that clearly met the inclusion criteria and we obtained the full text articles of potentially relevant references. Two review authors assessed the eligibility of retrieved papers independently (BWR and HK originally; BWR and TL for the 2012 update; and PH and LH for the 2015 update). We resolved disagreements by discussion and documented reasons for exclusion.

### Data extraction and management

We designed a specific data extraction form. For included studies, two review authors (BWR and HK) independently extracted data on characteristics of participants, the number of participants recruited to each arm, the completeness of surgical staging, the proportion of the different tumour stages and grades, the balance of prognostic factors achieved and interventions, the dose and duration of chemotherapy given in the treatment arm, study quality, duration of follow-up, outcomes, and any deviations from protocol. Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in the groups to which they were assigned. We noted the time points at which outcomes were collected and reported. We recorded any adverse effects reported in the studies. We resolved any disagreements by discussion between the review authors. We entered the data into Review Manager (RevMan) software ([RevMan 2014](#)) and checked data for accuracy. When information regarding any of the above was unclear, we attempted to contact the authors of the original reports to provide further details.

### Assessment of risk of bias in included studies

Two review authors (BWR and HK) independently assessed the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We assessed the following:

- selection bias (random sequence generation; allocation concealment);
- detection bias (blinding of outcome assessment);
- attrition bias (incomplete outcome data: we considered less than 20% attrition to be low risk);
- reporting bias (selective reporting of outcomes).

For further details see [Appendix 4](#).

### Measures of treatment effect

For time-to-event data (OS, DSS and PFS), we extracted the log HR and its variance from trial reports. If these were not given, we attempted to extract the data required to estimate them using Parmar's methods ([Parmar 1998](#)), e.g. number of events in each arm and log-rank P value comparing the relevant outcomes in each arm, or relevant data from Kaplan-Meier survival curves. If it was not possible to estimate the HR, we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of participants assessed per outcome (dichotomous data) in order to estimate a risk ratio (RR). We estimated the number needed to treat for an additional beneficial outcome (NNTB) by first performing a meta-analysis of the risk difference (RD) and then taking the inverse of the pooled RD.

For other dichotomous outcomes, e.g. adverse events, we extracted the number of patients in each treatment arm who were assessed at endpoint and the number who experienced the outcome of interest. We present dichotomous results as RRs with 95% CIs.

### Dealing with missing data

If studies did not report primary outcome data, we contacted the trial authors for additional data. The denominator for each outcome in each included trial was the number of participants randomised minus any participants whose outcomes were known to be missing.

### Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis by visual inspection of forest plots and by using the  $T^2$ ,  $I^2$  and  $\chi^2$  test statistics. We regarded heterogeneity as substantial if the  $I^2$  statistic was greater than 30% and either  $T^2$  was greater than zero, or there was a low P value (less than 0.10) in the  $\chi^2$  test for heterogeneity. If there was substantial heterogeneity, we investigated the possible reasons for it.

### Assessment of reporting biases

Where there were a sufficient number of included studies, we examined funnel plots corresponding to meta-analysis of the primary outcomes to assess the potential for publication bias. If these plots suggested that treatment effects were not sampled from a symmetric distribution, as assumed by the random-effects model (REM), we performed further meta-analyses using the fixed-effect model.

### Data synthesis

We carried out statistical analysis using Review Manager (RevMan) software ([RevMan 2011](#)). We pooled results of studies in a meta-analysis when clinically similar studies were available.

For time-to-event data, we pooled HRs using the generic inverse variance facility.

For any dichotomous outcomes (e.g. adverse events, and numbers of patients who relapsed or died, if it was not possible to treat these outcomes as time-to-event data), we pooled RRs.

We used the REM model for all meta-analyses ([DerSimonian 1986](#)).

If it was inappropriate to pool the data because of clinical heterogeneity, we performed a meta-analysis excluding outlying studies.

We created 'Summary of findings' tables in RevMan ([RevMan 2014](#)) with a summary of the intervention effect and a measure of quality produced for survival outcomes using the GRADE approach ([GRADEpro Guideline Development Tool \(GDT\)](#)). The GRADE approach uses five considerations to assess the quality of the body of evidence for each outcome. We downgraded the evidence from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

### Subgroup analysis and investigation of heterogeneity

We planned to do the following subgroup analyses:

- type of chemotherapy used; and
- optimal/suboptimal surgical staging, where optimal staging was defined as peritoneal staging plus retroperitoneal node assessment ([Table 1](#)).

We used the outcomes of OS and PFS in subgroup analyses. Since the only studies with data of satisfactory quality evaluated platinum-based chemotherapy, we did not perform subgroup analysis by type of chemotherapy. In addition, we had planned to perform additional subgroup analyses, to examine the influence of prognostic factors (e.g. clear cell histological subtype, degree of tumour differentiation) and dose of chemotherapy. However, this was not possible as data were not consistently reported by these subgroups in the included studies and we were unable to obtain individual patient data.

After publication of an abstract reporting the effect of adjuvant chemotherapy compared to no adjuvant chemotherapy in subgroups of high risk and intermediate/low risk stage I patients in the [ICON1 2003](#) trial, we decided to present these subgroup data in the 2012 version of the review. The definition of these subgroups was as follows:

- high risk: stage Ia grade 3, Ib or Ic grade 2 or 3, any clear cell tumour;
- intermediate risk: stage Ia grade 2, Ib or Ic grade 1; and
- low risk: stage Ia grade 1.

We had not specified subgrouping according to risk at the protocol stage of this review and we discuss this in the [Potential biases in the review process](#) section.

We assessed subgroup differences by interaction tests available within RevMan ([RevMan 2014](#)) and reported subgroup analyses results quoting the  $\chi^2$  test statistic and P value, and the interaction test  $I^2$  statistic value. We considered a P value of less than 0.05 to be statistically significant.

### Sensitivity analysis

We did not perform any sensitivity analyses since we considered all trials included in the meta-analyses to be at low risk of bias.

## RESULTS

### Description of studies

#### Results of the search

The search strategy up to August 2011 identified a total number of 3356 reference hits ([Figure 1](#)). After title and abstract screening of these references, we identified 31 citations (20 trials) as potentially eligible for this Cochrane review ([Table 2](#)). We performed full-text screening of these 31 references and excluded 17 reports relating to 15 trials for the reasons described in the '[Characteristics of excluded studies](#)' table. The remaining 14 reports (including conference abstracts) pertaining to five RCTs ([ACTION 2003](#); [Bolis 1995](#); [ICON1 2003](#); [Tropé 2000](#); [Young 1990](#)) met our inclusion criteria and we have described them in the '[Characteristics of included studies](#)' table.

For this 2015 review update, PH of the Netherlands Cochrane Centre searched the literature up to 24 March 2015. We identified and screened a total of 1080 references ([Figure 2](#)) and retrieved

10 full-text articles. Of these, one article met the inclusion criteria ([Collinson 2014](#)) and we excluded nine articles. The included article was a 10-year follow-up report of [ICON1 2003](#).

### Included studies

The five included studies, enrolling a total of 1277 women, compared immediate adjuvant chemotherapy with no immediate adjuvant chemotherapy ([Table 3](#)).

[Young 1990](#) was the first prospective RCT of adjuvant chemotherapy in early stage ovarian cancer to include a control group that had no immediate post-surgical treatment, with chemotherapy being reserved for treatment of disease recurrence. This trial was published in 1990, undertaken in the US, and was a joint effort of the Gynecologic Oncology Group and the Ovarian Cancer Study Group. The trial randomised women with FIGO 1976 stage Ia and Ib well-differentiated or moderately-differentiated tumours to receive either Melphalan 0.2 mg/kg or no chemotherapy. These women were surgically staged via a midline laparotomy to allow thorough assessment of the abdomen and pelvis. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy was performed and biopsies were taken of any peritoneal deposits. Random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment were also performed. This surgical staging routine is most likely to identify occult metastatic disease if present and therefore is optimal. This trial was flawed by the inclusion of 27 women with the Borderline Ovarian Tumour histological subtype though they were evenly distributed between the two trial arms.

The trial enrolled 92 women, randomising 48 to the chemotherapy arm and 44 to the observation-only arm. After randomisation, 11 women (five in the chemotherapy arm and six in the observation-only arm) were deemed ineligible and so 81 women (43 in the chemotherapy arm and 38 in the observation-only arm) were available for analysis. OS and disease-free survival (DFS) were reported at a median follow-up of six years. Six women died; two in the chemotherapy arm and four in the observation-only arm. Likewise, six women had disease recurrence; two in the chemotherapy arm and four in the observation-only arm. The trial authors reported no significant differences between treatment arms in either OS or DFS. Surviving women were followed up for a median of six years. The trial authors did not report HRs but presented Kaplan-Meier plots and log-rank P values for both OS and DFS, based on analysis of all eligible women regardless of the treatment they received. Minimum and maximum duration of follow-up were estimated from censoring marks on the Kaplan-Meier plots.

The trial authors reported adverse events in the adjuvant chemotherapy arm but did not assess adverse events in the no adjuvant chemotherapy arm.

[Bolis 1995](#) was an Italian multicentre RCT that recruited women with FIGO stage I epithelial ovarian cancer into two trial protocols. In trial 1, trial authors randomised women with stage Ia and Ib G2 and G3 to receive either cisplatin (50 mg/m<sup>2</sup>) for six cycles or to have no further therapy. The trial authors specified the inclusion of retroperitoneal (pelvic and para-aortic) nodal sampling in the protocol of this trial and therefore staging is optimal. In trial 2, trial authors compared cisplatin to intra-peritoneal radio-isotope in a

higher risk group of women; we did not include trial 2 in our review because it did not meet our inclusion criteria.

Trial 1 enrolled 85 women, randomising 41 to the chemotherapy arm and 44 to the observation-only arm. After randomisation, two women (both in the observation-only arm) were deemed ineligible and so 83 women (41 in the chemotherapy arm and 42 in the observation-only arm) were available for analysis. The trial reported OS and PFS. Seventeen women died; nine in the chemotherapy arm and eight in the observation-only arm. Twenty-one women had disease recurrence: seven in the chemotherapy arm and 14 in the observation-only arm. The trial authors reported no significant differences between treatment arms in either OS or PFS. The five-year DFS was 83% for women receiving cisplatin and 64% for the control group; the five-year OS was 87% and 81% in the cisplatin and control groups respectively. Trial authors followed up women for a median of 69 months.

The trial reported HRs for OS and PFS and their 95% CIs, adjusted for tumour grade. These were based on analysis of all eligible women according to the treatment allocated by randomisation.

The trial authors reported adverse events in the adjuvant chemotherapy arm but not in the no adjuvant chemotherapy arm.

**Tropé 2000** was a Scandinavian multicentre RCT in women with high-risk stage I epithelial ovarian cancer, which compared adjuvant carboplatin chemotherapy versus observation with treatment on clinical recurrence. The entry criteria for this trial were: FIGO stage I non-clear cell carcinoma G2 to G3 after a stipulated staging laparotomy via a midline incision with a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and an infracolic omentectomy. The trial authors obtained peritoneal washings and performed a thorough assessment of peritoneal surfaces with biopsy of any suspicious peritoneal or retroperitoneal lesions. The surgical staging protocol did not stipulate a systematic retroperitoneal lymphadenectomy although this was recommended as being optimal.

This trial had two aims, firstly to determine if there was a survival advantage for patients having adjuvant chemotherapy and secondly to test whether DNA ploidy was an independent prognostic factor in high-risk (non-clear cell) stage I epithelial ovarian cancer. The treatment protocol was with carboplatin intravenously dosed at AUC7 according to Calvert's formula (**Calvert 1989**) for six courses.

The trial included 175 women. After randomisation, the trial authors deemed 13 women ineligible and so 162 women (81 in each arm) were available for analysis. The trial reported DSS (i.e. survival of women who did not die of ovarian cancer or complications of treatment) and DFS. Eighteen women died of ovarian cancer; nine in both arms. Thirty-nine women had disease progression; 20 in the chemotherapy arm and 19 in the observation-only arm. The trial authors reported no significant differences between treatment arms in either DSS or PFS, and followed up women for a median of 46 months.

The trial reported unadjusted HRs for DSS and PFS and their 95% CIs. Multivariate Cox regression confirmed DNA ploidy, tumour grade and FIGO substage as independent prognostic determinants of DSS.

Adverse events were not reported.

**ICON1 2003** was a pragmatic trial of adjuvant platinum-based chemotherapy in women with early stage epithelial ovarian cancer. The trial recruited women from five countries: UK, Ireland, Brazil, Italy, and Switzerland. Computerised randomisation was done from offices in Milan and London. It was run alongside another collaborative trial, **ACTION 2003**, and reported simultaneously with it. It was pragmatic about the entry criteria as well as the treatment protocol. Clinicians were asked to recruit women with histologically confirmed invasive epithelial cancer in whom there was some uncertainty of the need for adjuvant chemotherapy. Most women (98%) had FIGO stage I disease, and the remainder had stage II disease. Thirteen per cent had FIGO stage Ia grade 1. Recommended surgical staging was less stringent in this trial than in the **ACTION 2003** trial, with the minimum requirement being for women to have had removal of all visible tumour with a total abdominal hysterectomy and bilateral salpingo-oophorectomy, where appropriate, and omentectomy. The minimal recommendation for 'peritoneal surgical staging' means that women were suboptimally staged in **ICON1 2003**.

Most women in the treatment group (87%) had carboplatin (AUC5), 11% had cisplatin in combinations, and a smaller percentage had other platinum-based regimens.

The trial enrolled 477 women, randomising 241 to the chemotherapy arm and 236 to the observation-only arm. Despite protocol violations, all analyses were on an ITT basis. The trial reported OS and RFS after five-year follow-up. One hundred and three women died; 42 in the chemotherapy arm and 61 in the observation-only arm. One hundred and seven women had disease recurrence: 47 in the chemotherapy arm and 60 in the observation-only arm. The trial authors reported a statistically significant benefit of chemotherapy in terms of both OS and RFS. The trial followed up surviving women for a median of 51 months and reported unadjusted HRs for OS and PFS and their 95% CIs (HR 0.66, 95% CI 0.45 to 0.97; and HR 0.65, 95% CI 0.46 to 0.91, respectively). Five-year survival was 79% among women who had chemotherapy compared to 70% among those who did not.

The trial reported adverse events in the adjuvant chemotherapy arm but not in the observation arm.

An abstract by **Swart 2007** initially reported the longer term follow-up of this trial and was robust to the five-year data. After median follow-up of 9.2 years, 144 women had died and 168 had disease recurrence. The abstract reported unadjusted HRs for OS and PFS and their 95% CIs (HR 0.74, 95% CI 0.53 to 1.02; and HR 0.70, 95% CI 0.52 to 0.95, respectively). Ten-year survival was 72% among women who had chemotherapy compared to 64% among those who did not. This abstract also reported the effect of adjuvant chemotherapy, subgrouped by level of risk, namely low/intermediate risk (Ia, G1 and G2, Ib or Ic, G1) and high risk (Ia, G3, Ib or Ic G2 or G3, any clear cell). Among the women at high risk, those who received adjuvant chemotherapy had significantly better OS and RFS than those who did not receive chemotherapy (HR 0.48, 95% CI 0.32 to 0.72; and HR 0.52, 95% CI: 0.33 to 0.82, respectively), whereas among the low/intermediate risk group, there was no significant difference in survival outcomes between treatment arms (HR 0.96, 95% CI: 0.54 to 1.66; and HR 0.96, 95% CI 0.50 to 1.38, respectively). **Collinson 2014** recently reported long term results, with a median follow-up of 10 years that was

completed in 2007. In the latter report, 165 women had experienced recurrence during the period and 151 had died.

**ACTION 2003** was a trial conducted at the same time as the **ICON1 2003** trial by the European Organisation for Research and Treatment of Cancer (EORTC) collaborators and recruited 448 women. This was a multicentre trial with centralised computer randomisation in Brussels. Nine countries recruited women between November 1990 and January 2000. Entry criteria were more stringent than in the **ICON1 2003** trial. The trial was open to women with stage Ia and Ib G2 and G3 (moderate and poorly differentiated tumours), and all stage Ic and stage Ia. Surgical staging was also specified and optimal staging to include pelvic and para-aortic retroperitoneal node dissection was strongly recommended. A pre-planned examination of the impact of surgical staging on survival outcome required careful documentation of surgical staging for each case, which was categorized as being inadequate, minimal, modified, or optimal.

The allowed chemotherapy regimens were single agent or combinations based on either cisplatin at 75 mg/m<sup>2</sup> or carboplatin at 350 mg/m<sup>2</sup>. Of the evaluable women who were randomised to receive chemotherapy, 47% had cisplatin in combination with cyclophosphamide and 33% had single-agent carboplatin. Women in the control group had no adjuvant treatment. They were followed up and chemotherapy reserved for cases of disease recurrence.

The trial enrolled 448 women, randomising 224 to each arm. Despite protocol violations, all analyses were on an ITT basis. The trial reported OS and RFS. Seventy-eight women died; 33 in the chemotherapy arm and 45 in the observation-only arm. One hundred women had disease recurrence; 40 in the chemotherapy arm and 60 in the observation-only arm. The trial authors reported a statistically significant benefit of chemotherapy in terms of RFS and a benefit in terms of OS which was not statistically significant. Women were followed up for a median of 5.5 years.

The trial reported unadjusted HRs for OS and RFS and their 95% CIs (HR 0.69, 95% CI 0.44 to 1.08; and HR 0.63, 95% CI 0.43 to 0.92, respectively). Five-year survival was 76% among women who had chemotherapy compared to 68% among those who did not. Multivariate Cox regression confirmed that staging adequacy and tumour grade were statistically significant prognostic factors for both OS and RFS.

Adverse events were not reported.

In a pre-planned subgroup analysis, the trial dichotomised staging adequacy into optimal and suboptimal groups. Among the 295 suboptimally staged women, the trial authors reported those who received adjuvant chemotherapy had significantly better OS and RFS than those who did not receive chemotherapy; whereas

among the 151 optimally staged women, there was no significant difference in survival outcomes between treatment arms.

Long-term results of this trial (median follow-up of 10.1 years) confirmed the original findings, that optimal surgical staging was associated with better outcomes and the survival benefits of adjuvant chemotherapy were limited to those women with suboptimal staging ([Trimbos 2010](#)). However, the 10-year follow-up report stated disease specific survival (DSS) instead of OS.

### Summary of included studies

Four included trials used cisplatin-based chemotherapy ([ACTION 2003](#); [Bolis 1995](#); [ICON1 2003](#); [Tropé 2000](#)), while one used melphalan ([Young 1990](#)). The trials had some important differences related to inclusion criteria, treatment arm protocols, trial size, and results statistic. The three oldest trials all recruited a small numbers of participants and so may have lacked the statistical power to detect a treatment effect even if one was present ([Bolis 1995](#); [Tropé 2000](#); [Young 1990](#)). In contrast, the two more recent trials, [ACTION 2003](#) and [ICON1 2003](#), were each much larger than preceding trials. Since they were run in parallel and reported in a joint analysis, the 'combined trial' had sufficient power to demonstrate a treatment effect. The [Bolis 1995](#) trial protocol specified examination of the retroperitoneal nodal groups at laparotomy in addition to peritoneal staging, and [Young 1990](#) specified sampling of pelvic and paraaortic lymph nodes; however, the [ICON1 2003](#) protocol made no such stipulation. As such the women in the latter trial were regarded to have been sub-optimally staged and may have included some women with occult advanced disease.

An important difference between [ACTION 2003](#) and the other trials was the predetermined intention of the trial authors to examine, in a subgroup, the effect of staging adequacy in either trial arm. Roughly one-third of the women recruited to this trial had more thorough surgical staging (described as optimal as opposed to adequate). This is an important difference because it is recognised that more thorough surgical staging (specifically retroperitoneal lymph node dissection) will result in a more accurate identification of women with occult advanced disease and women with disease confined to the ovary.

### Excluded studies

Of the 42 full-text references, we excluded 26 reports relating to 24 trials for the reasons described in the '[Characteristics of excluded studies](#)' table.

### Risk of bias in included studies

The included studies were of uniformly good quality (see [Characteristics of included studies](#) and [Figure 3](#)) except for [Young 1990](#) which had some inconsistencies in reporting (see [Effects of interventions](#) below).

**Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Blinding of outcome assessors (detection bias)	Selective reporting (reporting bias)
ACTION 2003	+	+	+	-	?
Bolis 1995	+	+	+	?	
ICON1 2003	+	+	+	-	
Tropé 2000	+	+	+		
Young 1990	+	+	+	?	?

All included studies reported adequate randomisation and adequate concealment of allocation. Consequently, [ACTION 2003](#), [ICON1 2003](#), [Tropé 2000](#) and [Young 1990](#) reported a balance of prognostic factors; however, [Bolis 1995](#) reported that women in the cisplatin arm were more likely to have poorly differentiated (G3) tumours and less likely to have clear cell histotype. [ACTION 2003](#) and [ICON1 2003](#) were not blinded, and blinding in the other included study was unclear. [ICON1 2003](#) reported no loss to follow-up after five years; one study, [ACTION 2003](#), reported 2% loss to follow-up after five years; [Tropé 2000](#) reported 7% of women were deemed ineligible after randomisation but that no further participants were lost to follow-up; and the remaining two studies reported 2% ([Bolis 1995](#)) and 12% ([Young 1990](#)) of women were deemed ineligible after randomisation but they did not report whether any subsequent loss to follow-up occurred.

We had some risk of bias concerns regarding the subgroup data for [ACTION 2003](#) and [ICON1 2003](#). [ACTION 2003](#) preferentially reported

DSS over OS in the 10-year follow-up report. In [ICON1 2003](#), low and intermediate risk data were combined in order to increase the power of the analysis but the effect of adjuvant treatment may have differed between these two risk groups. We were unable to obtain clarification from the [ICON1 2003](#) study authors regarding these concerns.

### Effects of interventions

See: [Summary of findings for the main comparison](#) [Summary of main findings](#)

Four studies reported OS ([ACTION 2003](#); [Bolis 1995](#); [ICON1 2003](#); [Young 1990](#)). One study reported PFS ([Bolis 1995](#)); two studies reported recurrence-free survival (RFS) ([ACTION 2003](#); [ICON1 2003](#)); two studies reported DFS ([Tropé 2000](#); [Young 1990](#)); for the purposes of meta-analysis, we assumed that these endpoints referred to the same outcome, measured in the same way, although

this may not necessarily be true (Altman 1995). One study reported disease-specific survival (DSS) (Tropé 2000), defined as survival until death from ovarian cancer or from complications of treatment for the disease, with deaths from other causes being censored, and ACTION 2003 reported DSS for the analysis of 10-year data.

We excluded Young 1990 from all meta-analyses since the data reported in the published report were not internally consistent: table 3 in the trial paper reported one disease recurrence in the chemotherapy group whereas figure 1 in the trial paper showed two disease recurrences in this group; table 3 reported deaths at 35 and 38 months in the chemotherapy group whereas figure 2 showed deaths at 38 and 75 months in this group. This study evaluated melphalan whereas all other included studies evaluated platinum-based chemotherapy.

The four studies we included in meta-analyses had similar median durations of follow-up: 66, 69, 51 and 46 months respectively (ACTION 2003; Bolis 1995; ICON1 2003; Tropé 2000). Two studies additionally reported the effect of adjuvant chemotherapy after 10 years' follow-up (ACTION 2003; ICON1 2003). In ICON1 2003 women were subgrouped by level of risk in a post-hoc analysis (Collinson 2014; Swart 2007; see Subgroup analysis and investigation of heterogeneity), whereas ACTION 2003 subgrouped women by the completeness of staging (optimal and non-optimal) in a pre-specified analysis (Trimbos 2010).

### Overall survival

Five-year OS was significantly better for women receiving adjuvant chemotherapy than for women in the observation group (1008 women, three studies; HR 0.71, 95% CI 0.53 to 0.93), with no heterogeneity between studies ( $I^2$  statistic = 0%). The studies contributing greatest weight to the analysis were ICON1 2003 (53%) and ACTION 2003 (39%) (Analysis 1.1).

The results of the 10-year OS meta-analysis (incorporating ICON1 2003 and ACTION 2003 data) were robust to the five-year findings and showed a significant difference between the two groups in favour of adjuvant chemotherapy (HR 0.72, 95% CI 0.57 to 0.92; 925 women, two studies;  $I^2$  statistic = 0%; Analysis 1.3). Overall, 25% (118/465) and 33% (152/460) of the women in the adjuvant chemotherapy group and observation groups, respectively, had died at a median follow-up of 10 years. Using these dichotomous data, the corresponding RR was 0.76 (95% CI 0.62 to 0.94; 923 women, two studies;  $I^2$  statistic = 0% (Analysis 1.4). We calculated that the number of women needed to treat for an additional beneficial outcome (NNTB) to prevent one death within 10 years was approximately 13 (95% CI 8 to 51).

### Progression-free survival

Meta-analysis showed significantly better PFS at five years in women receiving chemotherapy than in women who did not (1170 women, four studies; HR 0.67, 95% CI 0.53 to 0.84; Analysis 1.5), with no heterogeneity between studies ( $I^2$  statistic = 0%). Similarly, at 10 years, PFS was significantly better in the chemotherapy group (HR 0.67, 95% CI 0.53 to 0.83; 925 women, two studies;  $I^2$  statistic = 0%; Analysis 1.7). Overall, 28% (132/465) and 39% (181/460) of the women in the adjuvant chemotherapy group and observation groups, respectively, had experienced recurrence or had died at a median follow-up of 10 years (RR 0.72, 95% CI 0.60 to 0.87; 925 participants, two studies;  $I^2$  statistic = 0%; Analysis 1.8). We

calculated that the NNTB to prevent one recurrence or death within 10 years was approximately 10 (95% CI 7 to 20).

### Disease-specific survival

Only two studies reported this outcome; Tropé 2000 reported five-year DSS and ACTION 2003 reported 10-year DSS.

In Tropé 2000, there was no difference in DSS at five years between the adjuvant chemotherapy group and the observation group (HR 0.94, 95% CI 0.37 to 2.37; 162 women, one trial; Analysis 1.9). Ten-year follow-up data from ACTION 2003 similarly found no significant difference in DSS between the two groups overall (HR 0.73, 95% CI 0.47 to 1.13; Analysis 1.10).

### Subgroup analyses

We considered the following subgroup analyses to be of low to very low quality and should be interpreted with caution.

### Adequacy of surgical staging

#### Overall survival

We performed meta-analysis of three studies (ACTION 2003; Bolis 1995; ICON1 2003), subgrouped by optimal and suboptimal surgical staging. At a median follow-up of five years, the test for subgroup differences suggested that the effects of adjuvant chemotherapy compared with observation might differ between these subgroups, with no apparent additional benefit from adjuvant chemotherapy in the group that was optimally staged; however, subgroup differences were not statistically significant (Chi<sup>2</sup> test = 3.14, df = 1, P = 0.08;  $I^2$  statistic = 68.1%; Analysis 1.11).

ACTION 2003 reported 10-year DSS instead of OS and considered the findings robust to the five-year data. For the subgroup of suboptimally staged women, DSS was significantly better in the adjuvant chemotherapy group compared with observation (HR 0.58, 95% CI 0.35 to 0.96; 151 women, one trial; Analysis 1.12); whereas in the optimally staged group, chemotherapy provided no significant benefit over observation (HR 1.58, 95% CI 0.61 to 4.09; 151 women, one trial). However, the test for subgroup differences was not statistically significant (Test for subgroup differences: Chi<sup>2</sup> test = 3.32, df = 1; P = 0.07;  $I^2$  statistic = 69.9%). In this analysis we had risk of bias concerns about the preferential reporting of DSS instead of OS for 10-year follow-up. In addition, the number of events in the optimally staged subgroup was small. Therefore, we performed an exploratory analysis of 'deaths from ovarian cancer' at 10 years using dichotomous data from ACTION 2003 and ICON1 2003; this analysis suggested that the difference between subgroups in deaths from ovarian cancer was not statistically significant (Test for subgroup differences: Chi<sup>2</sup> test = 2.75, df = 1, P = 0.10;  $I^2$  statistic = 63.6%; Analysis 1.13).

#### Progression-free survival

We performed meta-analysis for PFS data at five years, subgrouped by optimal and suboptimal surgical staging. These subgroup analyses demonstrated no statistically significant difference in the effect of adjuvant chemotherapy compared with observation between subgroups at median follow-up of five and 10 years (Analysis 1.14; Analysis 1.15). An exploratory post-hoc analysis of 'progression of ovarian cancer' using 10 year dichotomous data from ACTION 2003 and ICON1 2003 were consistent with the PFS subgroup findings of no effect difference between subgroups (Analysis 1.16).

## Risk of disease progression

Only one trial ([ICON1 2003](#)) reported survival data subgrouped according to the level of risk. These subgroups were created post-hoc and we grouped treatment effects in women with low and intermediate risk disease together and compared with those in women with high-risk disease in order to increase the power of the analysis.

### Overall survival

At median 10-year follow-up, OS was improved with adjuvant chemotherapy among women with high-risk disease (HR 0.52, 95% CI 0.33 to 0.81; 216 participants, one trial) but the analysis was underpowered for low and intermediate risk disease. There was no statistically significant difference in treatment effect between risk groups ([Analysis 1.17](#); Test for subgroup differences: Chi<sup>2</sup> test = 2.08, df = 1, P = 0.15; I<sup>2</sup> statistic = 51.8%).

### Progression-free survival

At median 10-year follow-up, PFS was improved with adjuvant chemotherapy among women with high-risk disease (HR 0.48, 95% CI 0.32 to 0.73; 216 participants, one trial) but the analysis was underpowered for low and intermediate risk disease. There was no statistically significant difference in treatment effect between risk groups ([Analysis 1.18](#); Test for subgroup differences: Chi<sup>2</sup> test = 3.19, df = 1, P = 0.07; I<sup>2</sup> statistic = 68.6%).

### Adverse events

We were unable to compare the risk of adverse events in women who did and did not receive adjuvant chemotherapy, since none of the included studies reported adverse events among women who did not receive adjuvant chemotherapy.

### Assessment of reporting bias

We did not produce funnel plots for any outcomes as only four studies contributed data.

### Sensitivity analyses

We did not perform sensitivity analyses excluding poor quality studies since all studies reported adequate concealment of allocation and no studies reported blinding of outcome assessors.

### Exploratory analyses

We performed exploratory analyses on progression ([Analysis 1.19](#)) and death rates ([Analysis 1.20](#)). We subgrouped by risk to inform a prognostic table ([Table 4](#)).

## DISCUSSION

### Summary of main results

We included five RCTs ([ACTION 2003](#); [Bolis 1995](#); [ICON1 2003](#); [Tropé 2000](#); [Young 1990](#)), of which four studies evaluating platinum-based chemotherapy were of sufficient quality to contribute to meta-analysis ([ACTION 2003](#); [Bolis 1995](#); [ICON1 2003](#); [Tropé 2000](#); see 'Summary of findings' table 1). In total, 1170 women contributed data.

In women with early stage (FIGO I/IIa) epithelial ovarian cancer, those receiving adjuvant chemotherapy had a better five-year overall survival (OS) (HR 0.71, 95% CI 0.53 to 0.93) and PFS (HR

0.67, 95% CI 0.53 to 0.84) than those who did not receive adjuvant chemotherapy. At five-year follow-up, almost 30% fewer women in the adjuvant chemotherapy group had died compared with the observation group. However, between nine and 100 women would have to be treated with adjuvant chemotherapy to prevent one death and between seven and 33 women was the number needed to treat for an additional beneficial outcome (NNTB) to prevent one case of disease progression or recurrence. The survival benefit of chemotherapy was still evident at 10 years (two studies, 925 women; PFS: HR 0.67, 95% CI 0.53 to 0.83; OS: HR 0.72, 95% CI 0.57 to 0.92), for which the NNTB was 13 to prevent one death (95% CI 8 to 51), and 10 to prevent one recurrence (95% CI 7 to 20). We considered this evidence to be high quality according to the GRADE approach. Adjuvant chemotherapy benefited women who were suboptimally staged or those who had high risk disease. However, subgroup analyses could neither confirm nor exclude a benefit of adjuvant chemotherapy for optimally-staged women and women with low or intermediate risk disease at a median follow-up of 10 years.

### Overall completeness and applicability of evidence

The high number of women included in this Cochrane review gives clear and consistent evidence of the overall benefit of adjuvant chemotherapy for women with early stage ovarian cancer (FIGO stage I/IIa) on survival outcomes. Whilst the real value of adjuvant chemotherapy may be in the treatment of occult disease, we found insufficient evidence to confirm or exclude a beneficial effect in women who are optimally staged. It is likely that most women treated worldwide for early stage epithelial ovarian cancer are suboptimally staged, particularly since, even in [ACTION 2003](#) when comprehensive surgical staging was strongly advised, it was only performed in a third of women participating in the trial ([Timmers 2010](#)). Basing therapeutic management of early stage ovarian cancer on the adequacy of surgical staging is currently not supported by robust evidence and may not be clinically feasible given that the diagnosis of early stage ovarian cancer at the time of surgery is often not known.

It is important to note that the evidence relating to women with low and intermediate risk stage I ovarian cancer is incomplete. Few women in these studies had stage Ia grade 1 (low-risk disease) and we are very uncertain about whether the results of this review apply to this risk group. Furthermore, more evidence is needed to clarify to what extent adjuvant chemotherapy improves survival of women with intermediate-risk disease. Although certain subgroup findings suggested that there might be a difference in survival benefits according to extent of disease or risk, these may have been chance findings. It has been shown that if an overall treatment effect is statistically significant at the 5% level (as adjuvant chemotherapy is in our meta-analyses) and the women are divided at random into two similarly sized subgroups, then there is a one in three chance that the treatment effect will be large and statistically significant in one group but irrelevant and non-significant in the other ([Peto 1982](#)).

Unfortunately none of the included studies assessed the impact of adjuvant chemotherapy on the quality of life of the women. In addition, adverse events were poorly reported and did not use consistent definitions (e.g. [NCI CTCAE v3.0 2006](#)). Only three included studies reported adverse events in women receiving adjuvant chemotherapy ([Bolis 1995](#); [ICON1 2003](#); [Young 1990](#)); and no included studies reported adverse events in women who did

not receive adjuvant chemotherapy. To our knowledge, long term risks of adjuvant chemotherapy in ovarian cancer survivors have not been reported.

### Quality of the evidence

We considered the evidence for the primary outcomes, OS and PFS, to be of high quality (see 'Summary of findings' table 1), whereas we considered the quality of evidence relating to subgroup analyses to be low (for analyses according to risk) or very low (for analyses according to adequacy of staging).

With regard to subgroup findings according to surgical staging, the [ACTION 2003](#) trial was not designed to compare different surgical staging procedures, nor were women prospectively stratified by these categories. In addition, the numbers of women in the 'optimally staged' subgroup in meta-analyses were small. DSS was preferentially reported in the 10-year follow-up report, instead of OS, which was reported in the five-year follow-up report, and were not consistent with the PFS findings. Thus the findings for the subgroup analysis according to adequacy of surgical staging were ambiguous and we judged them to be very low quality.

For the subgroup findings according to risk, subgrouping in the contributing trial ([ICON1 2003](#)) was performed post-hoc. At the time of the previous update, only limited data were available in the form of a conference abstract ([Swart 2007](#)). Further evidence relating to these risk subgroups has now been published ([Collinson 2014](#)), which has not substantially changed the estimates of effect. However, a more complete data set including absolute number of events was available in [Collinson 2014](#). Although the trial authors stated that they had performed classification of trial participants into low, intermediate, and high risk groups before the dataset was locked for analysis, we had concerns that by combining the low risk group with the intermediate risk group to increase the power of the analysis they may have introduced bias into these analyses, and the analysis remained underpowered. We therefore judged the evidence from these subgroup analyses to be low quality.

### Potential biases in the review process

We conducted this Cochrane review according to the recommended Cochrane methodology to reduce the risk of bias in the review process. For the first update in 2012 ([Winter-Roach 2012](#)), we added a subgroup analysis by risk of recurrence/progression that we had not included in the original protocol of this review. By so doing, based on the [ICON1 2003](#) trial, we may have introduced a potential source of bias. Similarly, we assigned [Tropé 2000](#) and [Bolis 1995](#) to the 'optimal staging' subgroup and [ICON1 2003](#) to the 'sub-optimal staging' subgroup post hoc and subjectively.

In this update, we added meta-analysis of dichotomous survival data, and used these RRs to inform illustrative comparative risks ('Summary of findings' table 1) and Cates' plots. In addition, although we had not specified it in the protocol, we graded the subgroup evidence in order to illustrate our uncertainty in the quality of the subgroup evidence.

A limitation of the review protocol is that we did not include quality of life as an outcome.

### Agreements and disagreements with other studies or reviews

The role of chemotherapy in early stage epithelial ovarian cancer and the completeness of surgical staging in women with apparent early stage disease are interlinked issues and any discussion of the management of these women must consider both. There remains active debate in UK gynaecological oncology circles about lymphadenectomy in early stage epithelial ovarian cancer with many believing in the necessity of a systematic pelvic and para-aortic lymphadenectomy for accurate staging. This is because, when retroperitoneal lymph node dissection is not performed, there is a significant risk of failing to identify occult disease. Since the prognosis for women with para-aortic or pelvic node involvement is worse than for women with true stage I or II disease, any intervention trials with outcomes that group true early stage disease with occult stage IIIa disease will necessarily be very difficult to interpret. This may have been the case in [ICON1 2003](#), and a possible reason why the death rate at 10 years was relatively high in the low and intermediate risk group of this trial, at around 20%. However, [ICON1 2003](#) was a pragmatic trial and others may argue that it reflects the 'real life' scenario, where surgical staging is often inadequate in early stage disease.

NICE guidance on the diagnosis and initial treatment of women with ovarian cancer has taken a pragmatic line in its advice on the role of para-aortic node dissection in early stage disease ([NICE 2011](#)). It does not recommend systematic lymphadenectomy but rather advocates lymph node assessment by palpation and sampling of any suspiciously enlarged nodes. It argues that the morbidity of a comprehensive para-aortic lymphadenectomy cannot be justified. In which case, perhaps adjuvant chemotherapy in early stage disease is the lesser evil.

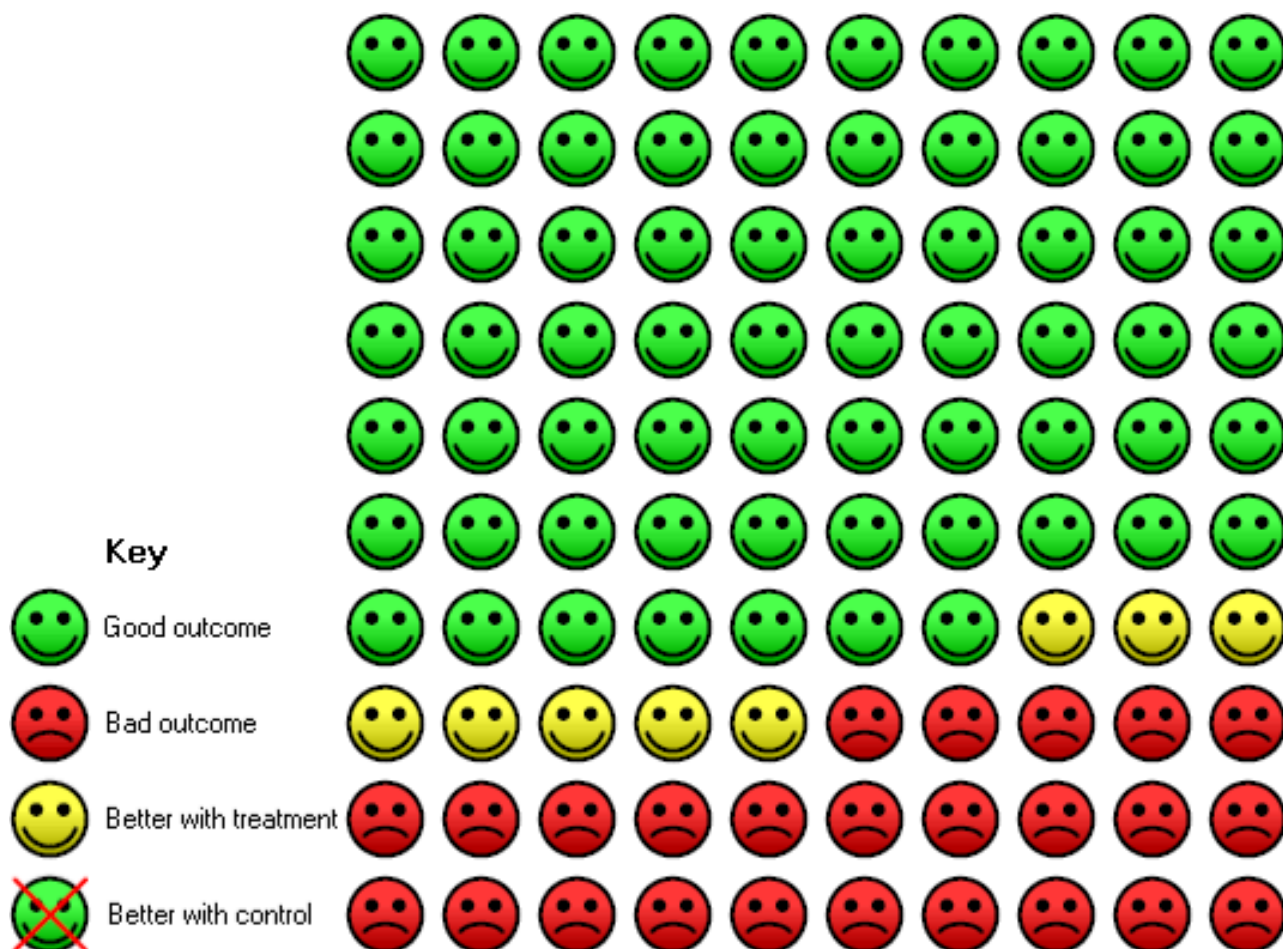
## AUTHORS' CONCLUSIONS

### Implications for practice

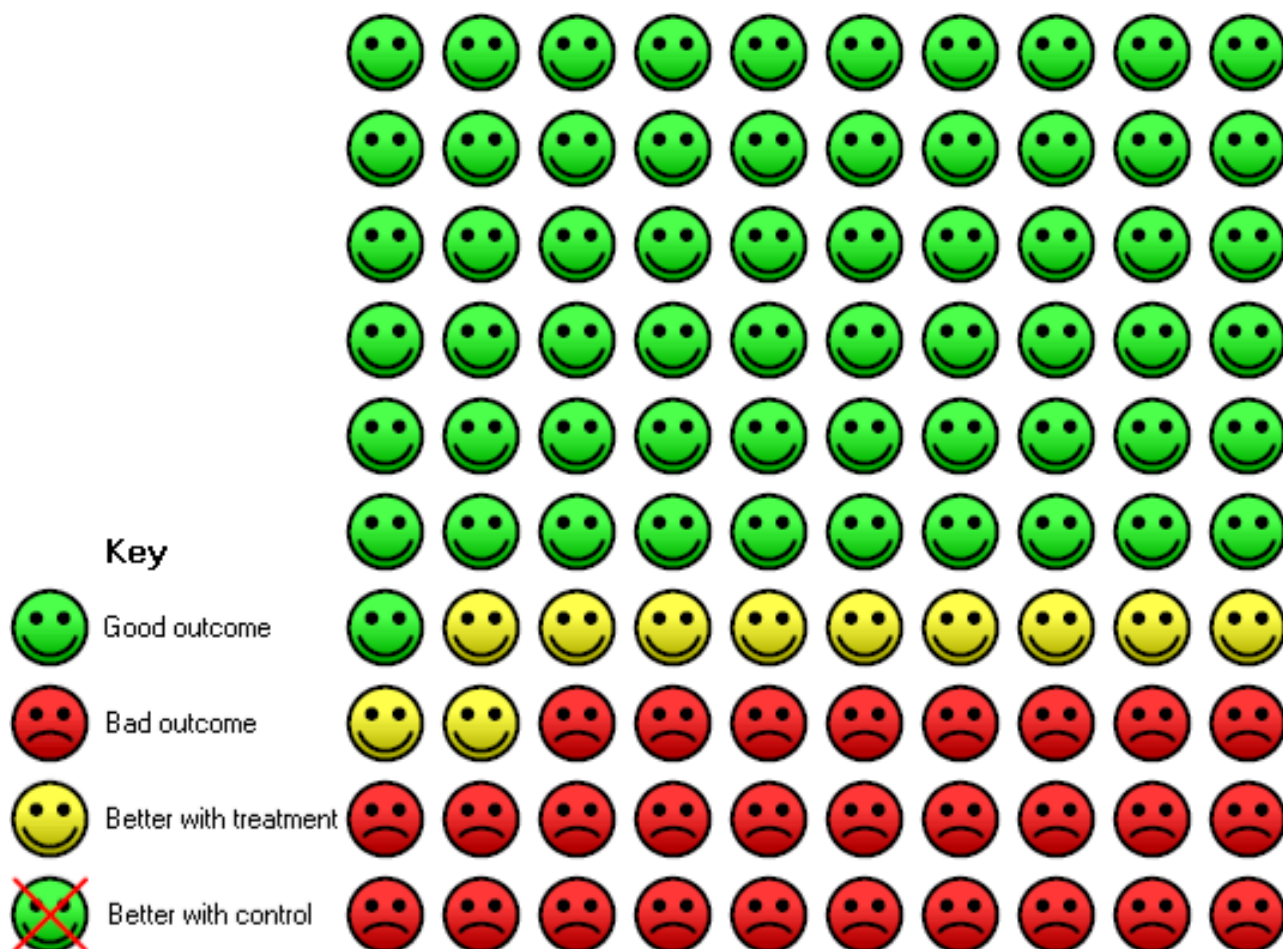
High quality evidence indicates that adjuvant platinum-based chemotherapy is effective in prolonging survival in women with early stage (FIGO stage I/IIa) epithelial ovarian cancer. Low quality evidence suggests that survival benefits may be greatest in women with high risk disease; however, uncertainty remains for lower risk early stage disease. Decisions to use AC in lower risk disease should be mindful of this uncertainty, and the uncertainty regarding adverse events, with treatment in lower risk disease individualised to take into account individual factors.

Cates plots may be helpful in counselling women about the relative survival benefits with adjuvant chemotherapy ([Figure 4](#); [Figure 5](#); [Figure 6](#); [Figure 7](#)).

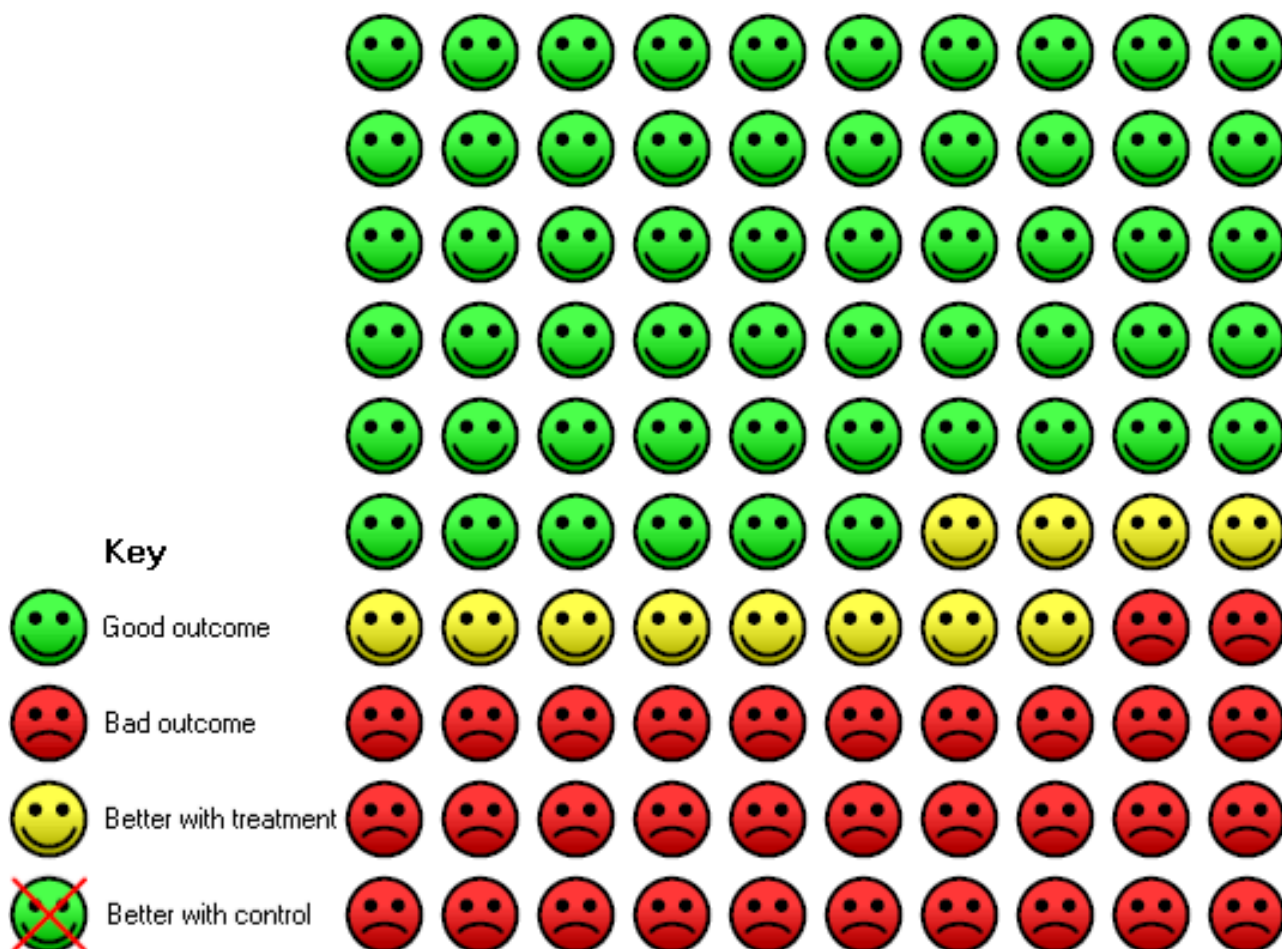
**Figure 4. Risk of death in the 10 years after surgery for women with early stage ovarian cancer treated with adjuvant chemotherapy: In the control group 33 women had died compared to 25 (20 to 31) out of 100 in the active treatment group.**



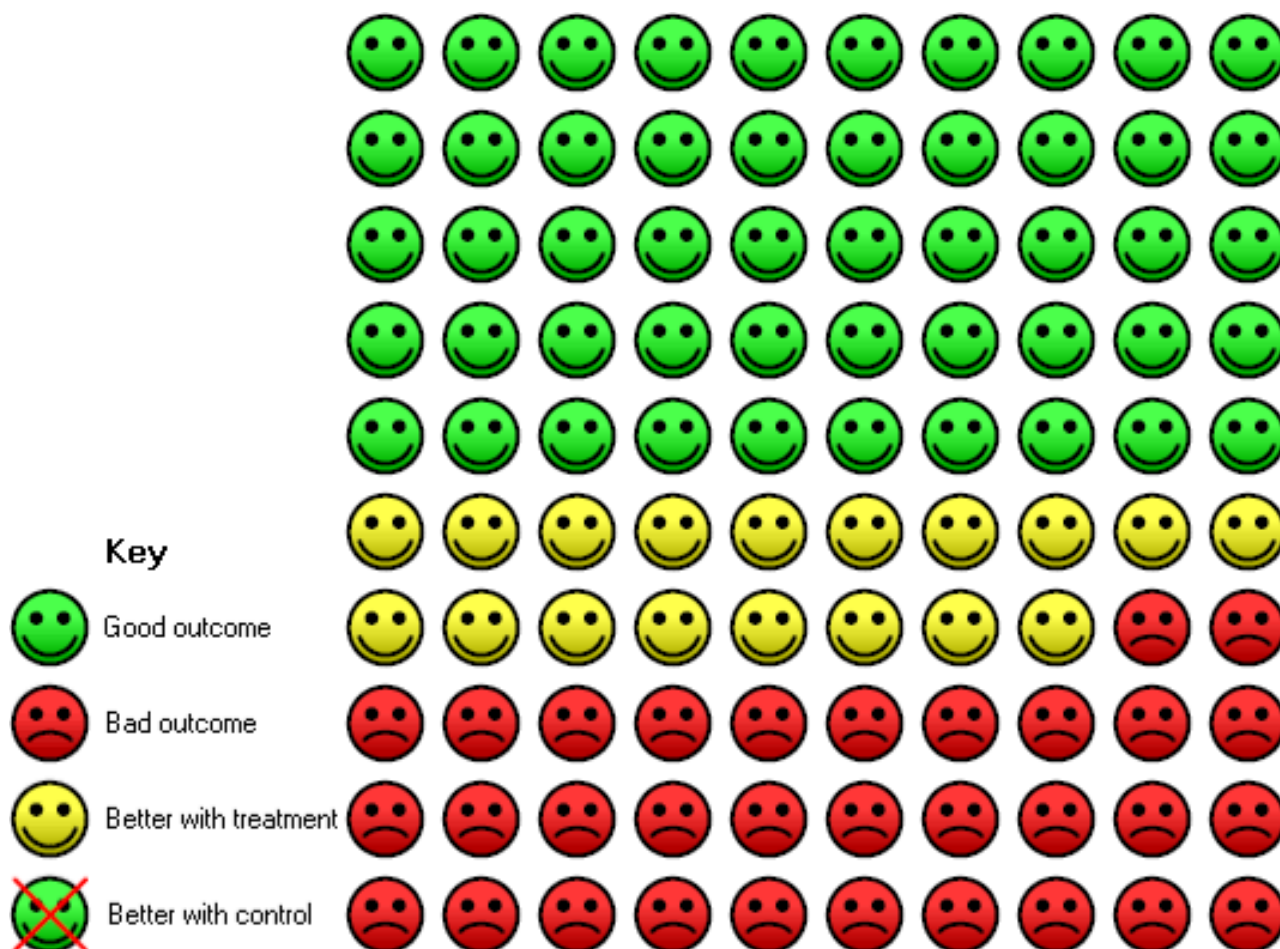
**Figure 5. Risk of cancer progression/recurrence in the 10 years after surgery for women with early stage ovarian cancer treated with adjuvant chemotherapy: in the control group 39 women had progressive disease compared to 28 (23 to 34) out of 100 in the active treatment group.**



**Figure 6. Risk of death in the 10 years after surgery for women with high risk early stage ovarian cancer treated with adjuvant chemotherapy: in the control group 44 people out of 100 died, compared to 32 (95% CI 23 to 43) out of 100 for the active treatment group.**



**Figure 7. Risk of cancer progression/recurrence in the 10 years after surgery for women with high risk early stage ovarian cancer treated with adjuvant chemotherapy: in the control group 50 women had progressive disease compared to 32 (23 to 45) out of 100 in the active treatment group.**



### Implications for research

It is remarkable that two reasonably large studies have reported 10-year follow-up data and it is possible that even longer follow-up could be attempted. Fifteen year follow-up data could shed further light on survival as well as potential long term risks of adjuvant chemotherapy, including secondary cancers. [ACTION 2003](#) investigators might consider conducting subgroup analysis by risk. In addition, meta-analysis of individual patient data (IPD) if made available by [ACTION 2003](#) and [ICON1 2003](#) could help to confirm or exclude subgroup differences.

There are still deficiencies in the evidence which can be addressed in the context of a collaborative trial. The [ACTION 2003](#) investigators have proposed a trial in which women who are suboptimally staged are randomised either to have a staging laparotomy or to have adjuvant chemotherapy. The trial authors propose a trial in apparent early ovarian cancer with two levels of randomisation; the first step would randomise participants to either optimal staging or peritoneal staging. The trial would recommend adjuvant chemotherapy to all patients with high-grade tumours. In the second step, the trial would randomly assign women with 'low risk' histology in the peritoneal staging arm to either adjuvant chemotherapy or observation and would observe those optimally

staged. Such a trial would evaluate firstly whether there is a survival advantage to retroperitoneal node sampling in early stage ovarian cancer and secondly whether a group of women with early stage epithelial ovarian cancer can safely be managed without adjuvant chemotherapy. However, phase 3 trials of early ovarian cancer are difficult to conduct because of the relatively small number of women with early stage disease. Consensus from the 4th Ovarian Cancer Conference of the Gynaecologic Cancer InterGroup recommends that the primary endpoint for these trials is therefore RFS ([Thigpen 2011](#)). FIGO staging was updated in January 2014 to subdivide stage 1C and abolish stage IIC altogether. This doesn't affect the results of this report, but will impact on studies of early stage disease in the future.

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## References to other published versions of this review

### Winter-Roach 2009

Winter-Roach BA, Kitchener HC, Dickinson HO. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: [10.1002/14651858.CD004706.pub2](https://doi.org/10.1002/14651858.CD004706.pub2)]

### Winter-Roach 2012

Winter-Roach BA, Kitchener HC, Lawrie TA. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: [10.1002/14651858.CD004706.pub4](https://doi.org/10.1002/14651858.CD004706.pub4)]

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### ACTION 2003

Methods	Multicentre RCT
Participants	448 FIGO Ia-Ib G2/3, FIGO Ic-IIa, FIGO I-IIa clear cell Stage 1 a-1c (93%), IIa (7%) G1 (12%), G2 (51%), G3 (35%)
Interventions	Immediate platinum-based chemotherapy versus treatment on progression Cisplatin dose = 75 mg/m <sup>2</sup> Carboplatin dose = 350 mg/m <sup>2</sup>
Outcomes	DFS and OS Adverse events not reported Median follow-up: 5.5 years
Notes	Subgroup analysis examined impact of staging adequacy

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Based on minimisation.
Allocation concealment (selection bias)	Low risk	Minimisation performed by central co-ordinating centres.
Incomplete outcome data (attrition bias) All outcomes	Low risk	T: 6/224 (2%) C: 3/224 (1%)
Blinding of outcome assessors (detection bias)	High risk	No blinding
Selective reporting (reporting bias)	Unclear risk	Intention-to-treat (ITT) analysis; all pre-specified outcomes reported.  DSS appears to be preferentially reported over OS in the 10-year follow-up report of subgroup data according to the adequacy of surgical staging, and is not consistent with the RFS data.

#### Bolis 1995

Methods	RCT
Participants	85 FIGO (1976) IA-IB Grade 2 and 3
Interventions	Cisplatin 50 mg/m <sup>2</sup> x 6 cycles Q 28/7 versus observation
Outcomes	DFS 83% versus 64%

#### Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer (Review)

## Bolis 1995 (Continued)

OS 88% versus 82%

Adverse events in adjuvant chemotherapy arm: nausea and vomiting in more than 2/3 of patients; but in severe form in less than 10% of courses; leukopenia and thrombocytopenia in 14% of patients but  $\geq$  Grade 3 in only 1% of patients; no episodes of febrile infection

Adverse events in no adjuvant chemotherapy arm: not reported  
Median follow-up: 69 months

Notes Patients with residual disease in both arms

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Blinding of outcome assessors (detection bias)	Unclear risk	Not reported.

## ICON1 2003

Methods	Multicentre RCT
Participants	447 FIGO I-III 93% FIGO stage I  Low-risk defined as stage Ia, G1 (13%); intermediate risk defined as stage Ia, G2 and stage Ib/Ic G1 (38%); high risk defined as stage Ib/Ic grade 2/3 or any stage I grade 3 or clear cell histology (47%)
Interventions	Immediate platinum-based chemotherapy versus treatment on progression
Outcomes	DFS and OS  Adverse events in adjuvant chemotherapy arm: 63/241 (26%) experienced toxicity sufficient to require modification of treatment Adverse events in no adjuvant chemotherapy arm: not reported  Median follow-up of surviving women: 51 months (Colombo 2003) Median follow-up: 9.2 years (Swart 2007)  Median follow-up: 10 years (Collinson 2014)
Notes	Long-term follow-up examined subgroup differences according to risk. Low- and intermediate-risk data were combined due to a lack of power "without reference to outcomes". The risk groups were pre-specified "before the data set lock for analyses". We were unable to obtain clarification from the trial authors regarding the effect of combining low risk with intermediate risk on the estimates.

### Risk of bias

**ICON1 2003** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Blinding of outcome assessors (detection bias)	High risk	

**Tropé 2000**

Methods	RCT
Participants	162 high risk FIGO stage I
Interventions	Carboplatin 6 cycles Q28/7 AUC = 7 versus treatment at progression
Outcomes	DFS and OS  Adverse events not reported  Median follow-up: 46 months
Notes	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

**Young 1990**

Methods	RCT
Participants	92 FIGO stage I
Interventions	Melphalan chemotherapy versus treatment on progression

## Young 1990 (Continued)

Outcomes	DFS and OS	
	Adverse events in adjuvant chemotherapy arm: 79% had some degree of myelosuppression; 7 patients (16%) had severe myelosuppression; 5 patients (12%) had platelet count nadirs under 50,000 platelets/mm <sup>3</sup> ; 4 patients (9%) had platelet count nadirs under 2000 platelets/mm <sup>3</sup> ; no infectious complications related to leukopenia; no bleeding episodes related to thrombocytopenia induced by chemotherapy. Eleven patients (26%) reported mild-to-moderate gastric gastrointestinal side effects. No other adverse effects were reported. One patient died 6 years after completing treatment, with a diagnosis of aplastic anaemia; no other myeloprolific disorders or second cancers were seen after > 250 person-years follow-up.	
	Adverse events in no adjuvant chemotherapy arm: not reported	
	Median follow-up of surviving women: 6 years	
Notes	Melphalan produced severe myelosuppression	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Based on computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Central randomisation by telephone call to co-ordinating centre.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Deemed ineligible after randomisation: T: 5/48 (10%) C: 6/44 (14%)  Did not report whether any further loss to follow-up occurred
Blinding of outcome assessors (detection bias)	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	ITT analysis; adverse events in 'no adjuvant chemotherapy' arm not reported.

Abbreviations: AUC = area under curve; C = control; DFS = disease-free survival; ITT = intention-to-treat; OS = overall survival; T = treatment; DSS = Disease-specific survival; RFS = recurrence-free survival

## Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
<a href="#">Bapsy 2012</a>	Not a RCT.
<a href="#">Bookman 2011</a>	Not a RCT.
<a href="#">Burger 2012</a>	Not a RCT.
<a href="#">Cascales 2011</a>	Not a RCT.
<a href="#">Chiara 1994</a>	This RCT compared whole abdominal radiotherapy (WAR) versus cyclophosphamide, adriamycin, and cisplatin (CAP) chemotherapy.

Study	Reason for exclusion
Cliby 2013	Not a RCT.
Cui 2012	Not a RCT.
Dembo 1979	A RCT of radiotherapy versus radiotherapy plus chlorambucil.
Fujiwara 2012	Not a RCT.
Geurts 2011	Not a RCT.
Grönroos 1984	Quasi-randomised trial (by birth month) comparing single or combined chemotherapy agents with radiotherapy or surgery alone in women with epithelial ovarian cancer stages I to IV. Included 150 women with stage I/II epithelial ovarian cancer randomised to 3 groups (surgery only, surgery + chemotherapy (CT), or surgery + radiotherapy (RT)). Followed up for 3 years.
Hreshchyshyn 1980	This trial compared chemotherapy against radiotherapy and no further treatment. It did not specify the method of randomisation and a prognostic balance was not achieved in the different trial arms.
Klaassen 1988	This trial compared 3 different adjuvant treatments all given after pelvic radiotherapy: melphalan, whole abdominal radiotherapy, and intraperitoneal radio-isotope therapy.
Kojs 2001	This trial compared adjuvant whole abdominal radiotherapy with CAP.
Maggioni 2006	This was a trial comparing systematic lymphadenectomy with lymph node sampling in apparent early stage ovarian cancer; it was not a trial of adjuvant treatment.
Mannel 2011	A randomised trial of maintenance low-dose paclitaxel for 24 weeks versus observation, in completely resected early-stage ovarian cancer patients receiving 3 cycles of chemotherapy (CP). The trial is also known as GOG 175.
Sell 1990	This trial compared whole abdominal radiotherapy to a combination of pelvic radiotherapy and cyclophosphamide. Additionally the block randomisation method did not achieve prognostic balance between the 2 trial arms.
Sevelde 1987	This was a trial of adjuvant radiotherapy versus adjuvant chemo-irradiation in women with early stage ovarian cancer.
Sigurdsson 1982	This trial compared melphalan chemotherapy to observation for mucinous stage Ia and Ib tumours, chemotherapy versus radiotherapy compared for non-mucinous stage Ia and Ib, and radiotherapy versus chemo-radiotherapy in stage Ic to IIc. There was a stratified quasi-randomisation which did not achieve prognostic balance between the various trial arms.
Smith 1975	This trial compared melphalan chemotherapy versus whole abdominal radiotherapy; the method of randomisation was unspecified and more patients with stage 1 disease were in the chemotherapy arm.
Vergote 1992	This was a methodologically good trial with central computerised randomisation; it compared chemotherapy with intraperitoneal radio-isotope therapy.
von Greunigen 2012	A RCT of adjuvant chemotherapy in women with advanced (stage III) ovarian cancer.
Young 2000	The comparison was between 3 and 6 cycles of platinum-based adjuvant chemotherapy.
Young 2003	This trial compared intraperitoneal radio-isotope therapy with cyclophosphamide and cisplatin chemotherapy after surgery in early stage disease; there was no control arm on observation only.

Abbreviations: CAP = cyclophosphamide, adriamycin and cisplatin; CT = chemotherapy; RCT = randomised controlled trial; RT = radiotherapy.

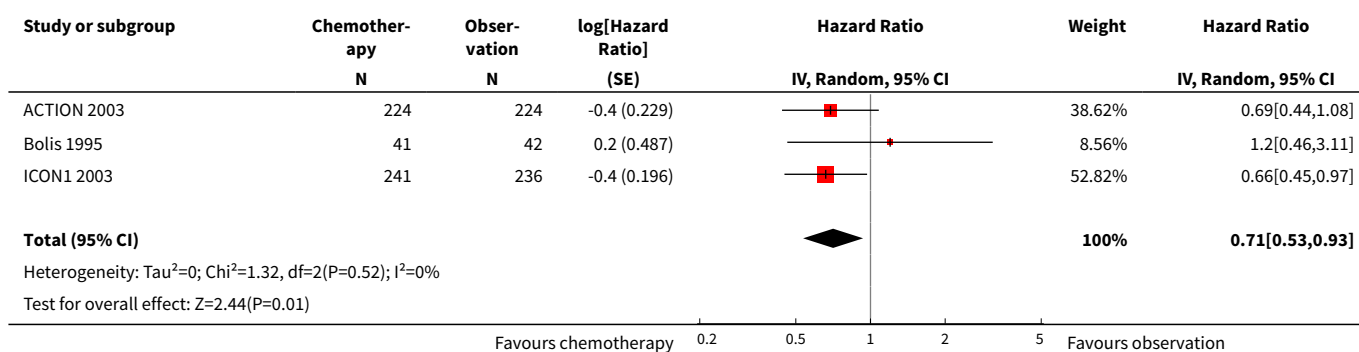
## DATA AND ANALYSES

### Comparison 1. Adjuvant chemotherapy versus observation

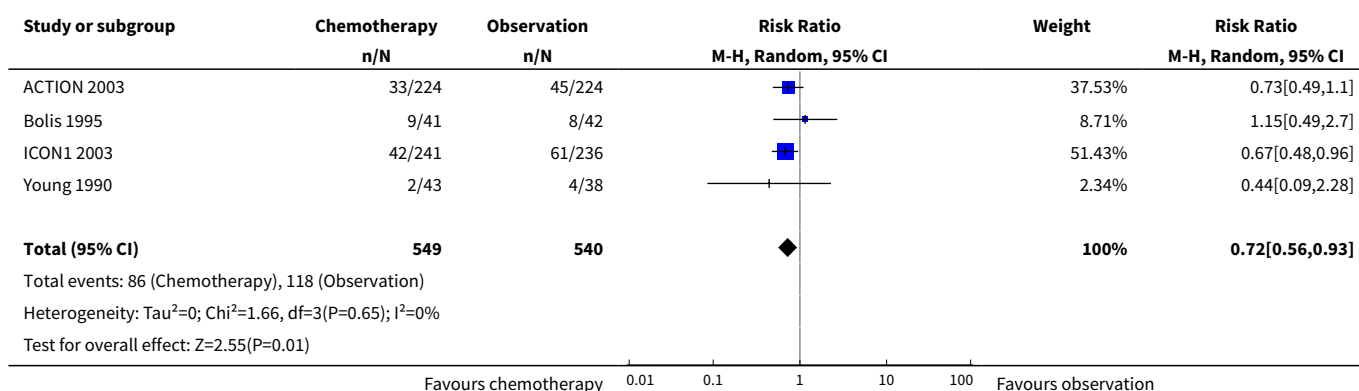
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival (5 yr)	3	1008	Hazard Ratio (Random, 95% CI)	0.71 [0.53, 0.93]
2 Deaths total (5 yr)	4	1089	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.93]
3 Overall survival (10 yr)	2	925	Hazard Ratio (Random, 95% CI)	0.72 [0.57, 0.92]
4 Death total (10 yr)	2	923	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.62, 0.94]
5 Progression-free survival (5 yr)	4	1170	Hazard Ratio (Random, 95% CI)	0.67 [0.53, 0.84]
6 Progression total (5 yr)	4	1089	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.57, 0.84]
7 Progression-free survival (10 yr)	2	925	Hazard Ratio (Random, 95% CI)	0.67 [0.53, 0.83]
8 Progression total (10 yr)	2	925	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.60, 0.87]
9 Disease-specific survival (5 yr)	1		Hazard Ratio (Random, 95% CI)	Subtotals only
10 Disease-specific survival (10 yr)	1		Hazard Ratio (Random, 95% CI)	Subtotals only
11 Subgroup analysis by staging: 5-yr OS	3		Hazard Ratio (Random, 95% CI)	Subtotals only
11.1 Optimal staging	2	234	Hazard Ratio (Random, 95% CI)	1.22 [0.63, 2.37]
11.2 Suboptimal staging	2	772	Hazard Ratio (Random, 95% CI)	0.63 [0.46, 0.85]
12 Subgroup analysis by staging: 10 yr DSS	1		Hazard Ratio (Random, 95% CI)	Subtotals only
12.1 Optimal staging	1	151	Hazard Ratio (Random, 95% CI)	1.58 [0.61, 4.09]
12.2 Suboptimal staging	1	295	Hazard Ratio (Random, 95% CI)	0.58 [0.35, 0.96]
13 Subgroup analysis by staging: death from ovarian cancer (10 years)	2	923	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.54, 1.12]
13.1 Optimal staging	1	151	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.64, 3.79]
13.2 Suboptimal staging	2	772	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.54, 0.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">14 Subgroup analysis by staging: 5-yr PFS</a>	4	1168	Hazard Ratio (Random, 95% CI)	0.64 [0.52, 0.78]
14.1 Optimal staging	2	234	Hazard Ratio (Random, 95% CI)	0.67 [0.36, 1.22]
14.2 Suboptimal staging	3	934	Hazard Ratio (Random, 95% CI)	0.64 [0.50, 0.82]
<a href="#">15 Subgroup analysis by staging: 10-yr PFS</a>	2	923	Hazard Ratio (Random, 95% CI)	0.66 [0.53, 0.83]
15.1 Optimal staging	1	151	Hazard Ratio (Random, 95% CI)	0.73 [0.38, 1.42]
15.2 Suboptimal staging	2	772	Hazard Ratio (Random, 95% CI)	0.65 [0.52, 0.83]
<a href="#">16 Subgroup analysis by staging: progression of ovarian cancer (10 years)</a>	2	923	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.87]
16.1 Optimal staging	1	151	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.39, 1.26]
16.2 Suboptimal staging	2	772	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.88]
<a href="#">17 Subgroup analysis by risk: 10-yr OS</a>	1	414	Hazard Ratio (Random, 95% CI)	0.66 [0.38, 1.13]
17.1 Low/intermediate risk	1	198	Hazard Ratio (Random, 95% CI)	0.91 [0.49, 1.69]
17.2 High risk	1	216	Hazard Ratio (Random, 95% CI)	0.52 [0.33, 0.81]
<a href="#">18 Subgroup analysis by risk: 10-yr PFS</a>	1	414	Hazard Ratio (Random, 95% CI)	0.64 [0.34, 1.21]
18.1 Low/medium	1	198	Hazard Ratio (Random, 95% CI)	0.92 [0.52, 1.64]
18.2 High	1	216	Hazard Ratio (Random, 95% CI)	0.48 [0.32, 0.73]
<a href="#">19 Subgroup analysis by risk: progression at 10 yrs</a>	1	414	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.53, 0.95]
19.1 Low/intermediate risk	1	198	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.53, 1.46]
19.2 High risk	1	216	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.46, 0.90]
<a href="#">20 Subgroup analysis by risk: deaths by 10 yrs</a>	1	414	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.53, 0.98]
20.1 Low/intermediate risk	1	198	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.50, 1.51]
20.2 High risk	1	216	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.47, 0.96]

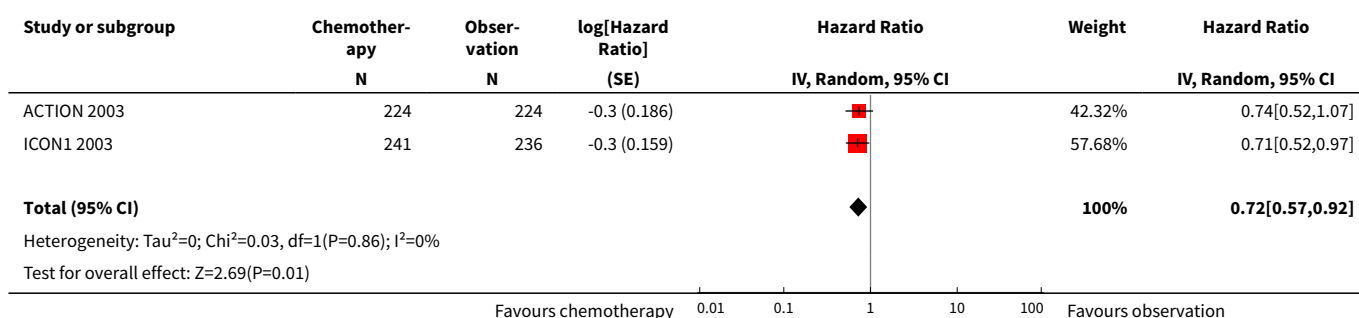
### Analysis 1.1. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 1 Overall survival (5 yr).



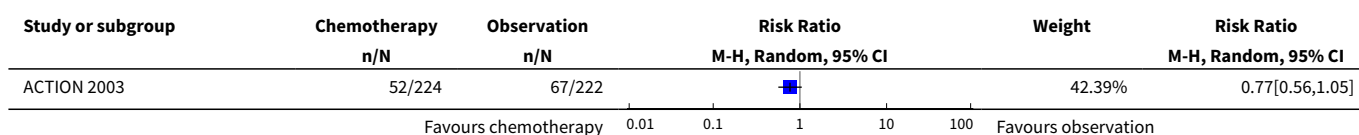
### Analysis 1.2. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 2 Deaths total (5 yr).

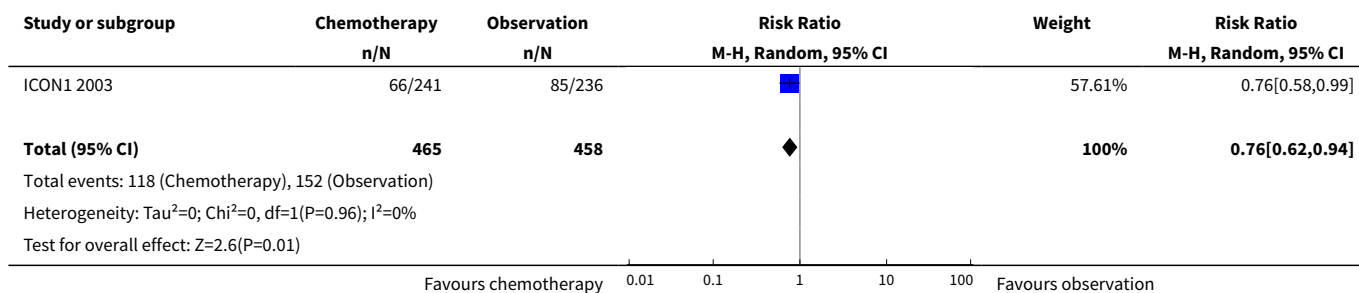
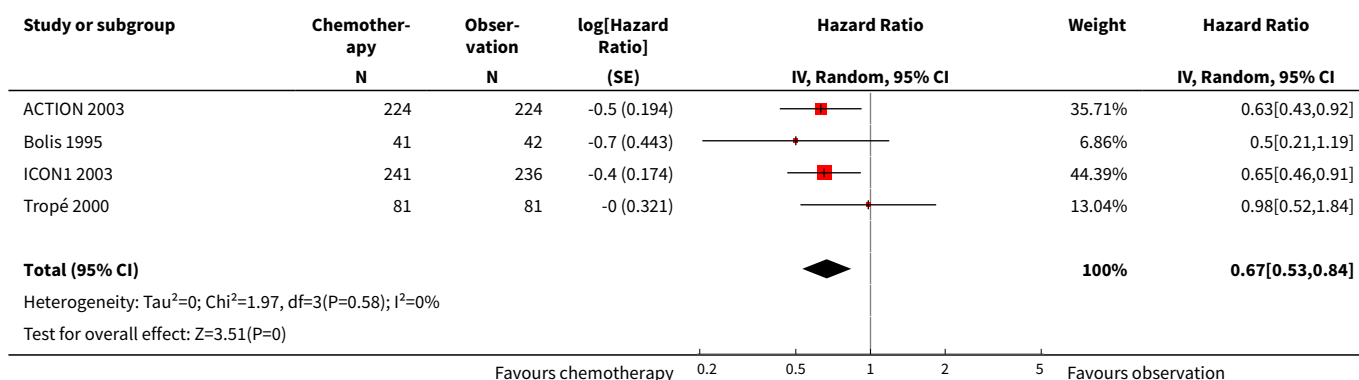
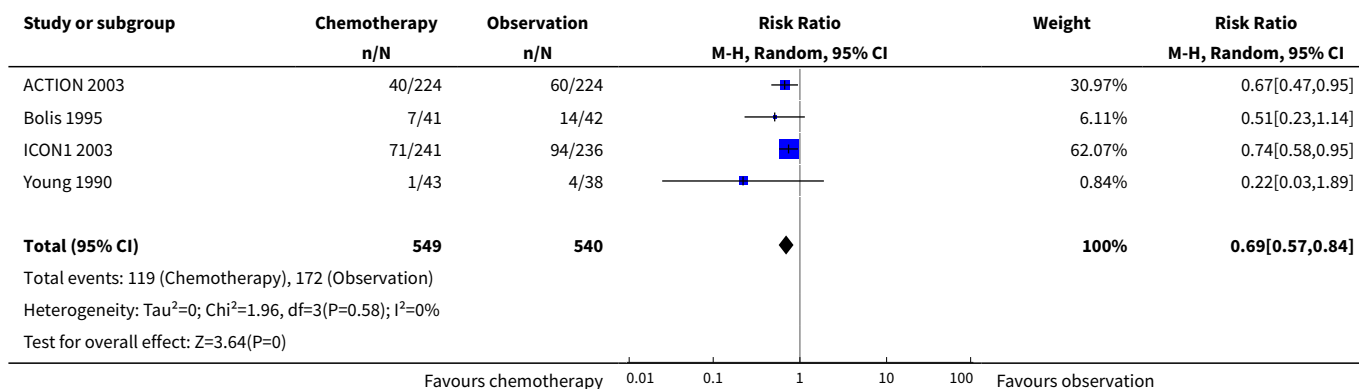
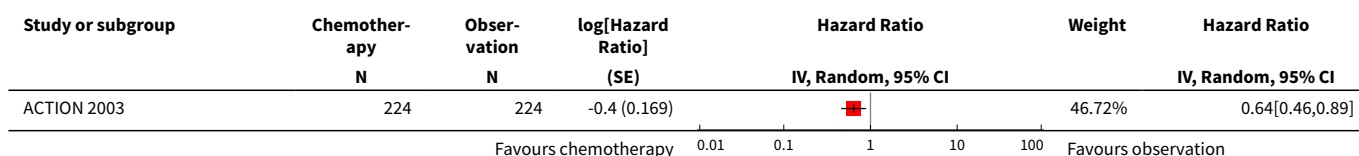


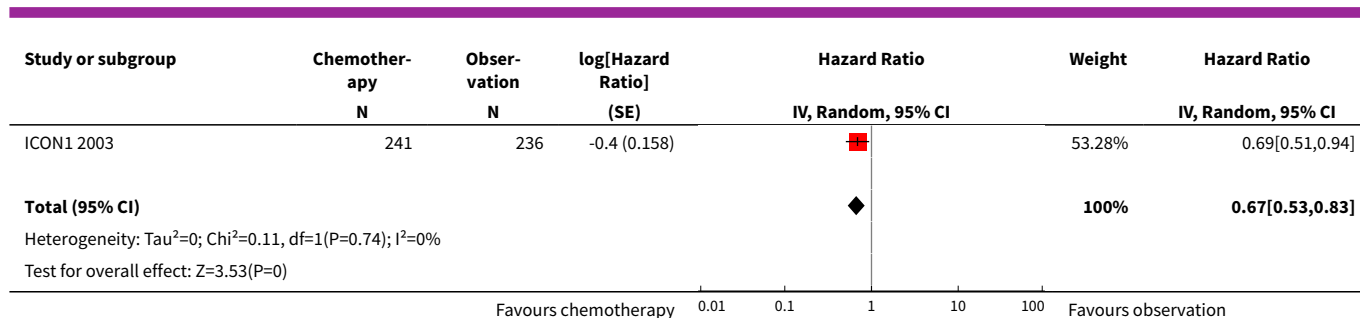
### Analysis 1.3. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 3 Overall survival (10 yr).



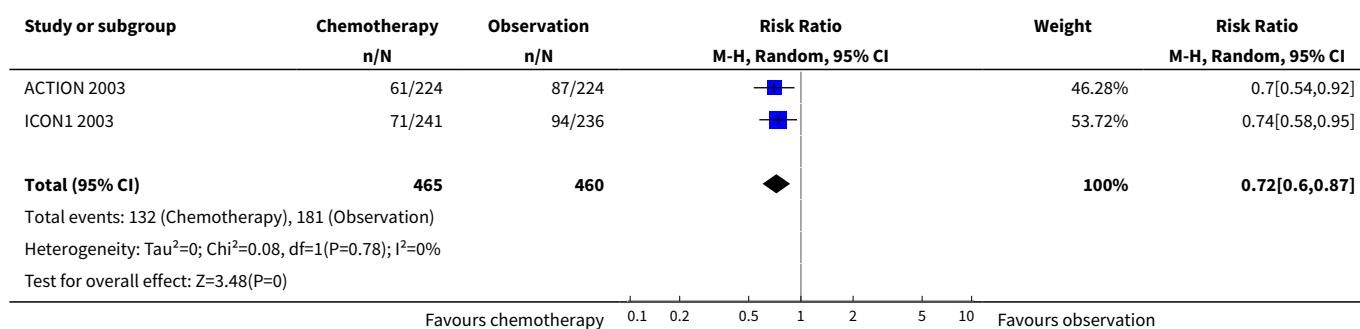
### Analysis 1.4. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 4 Death total (10 yr).



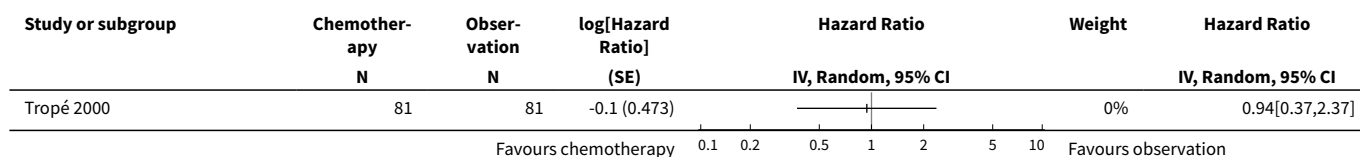
**Analysis 1.5. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 5 Progression-free survival (5 yr).****Analysis 1.6. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 6 Progression total (5 yr).****Analysis 1.7. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 7 Progression-free survival (10 yr).**



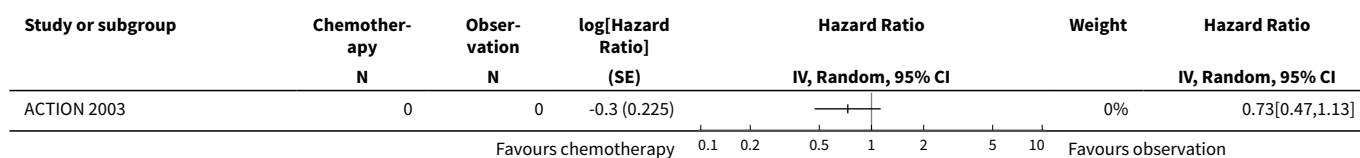
### Analysis 1.8. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 8 Progression total (10 yr).



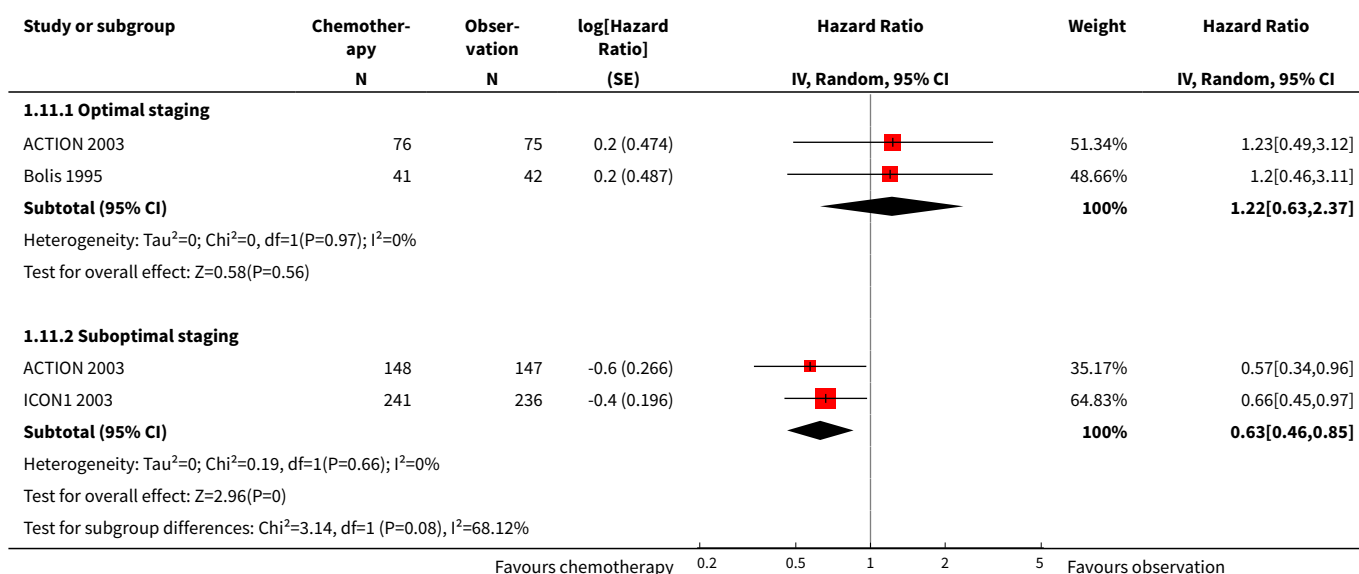
### Analysis 1.9. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 9 Disease-specific survival (5 yr).



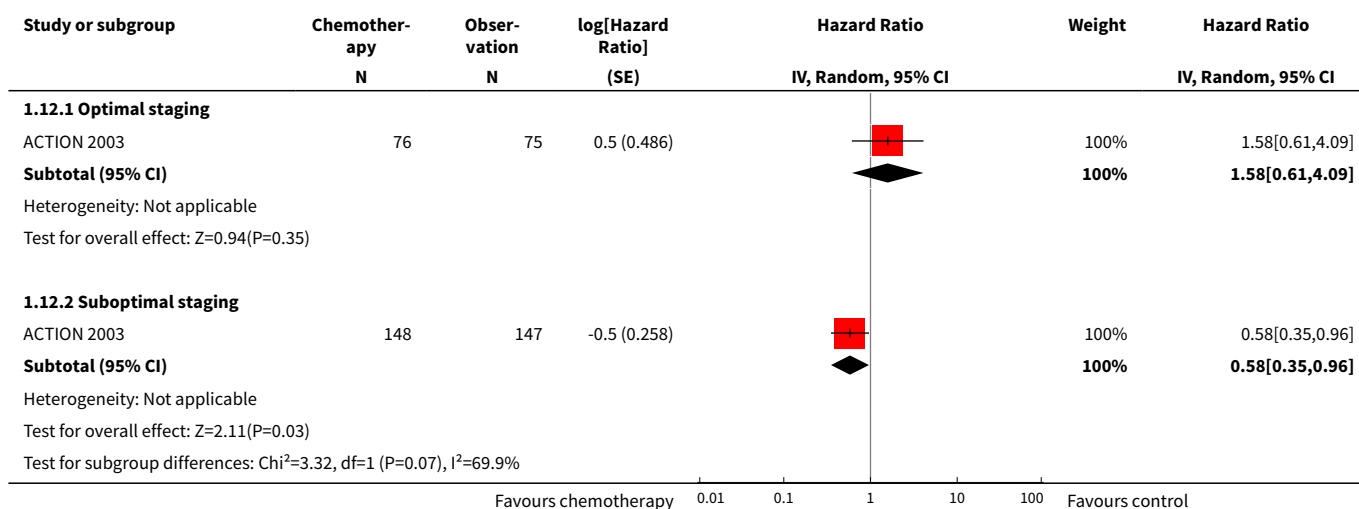
### Analysis 1.10. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 10 Disease-specific survival (10 yr).



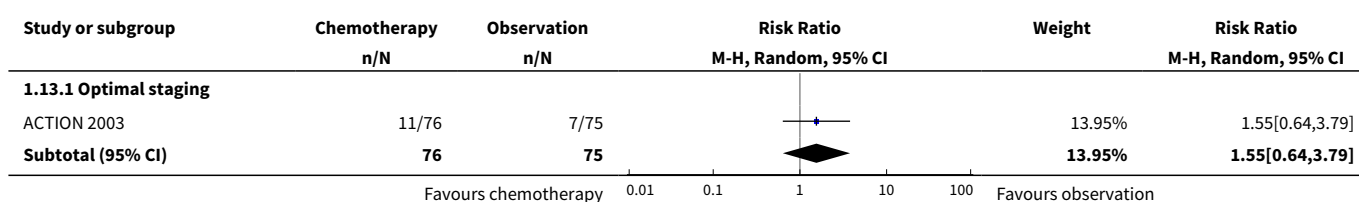
### Analysis 1.11. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 11 Subgroup analysis by staging: 5-yr OS.

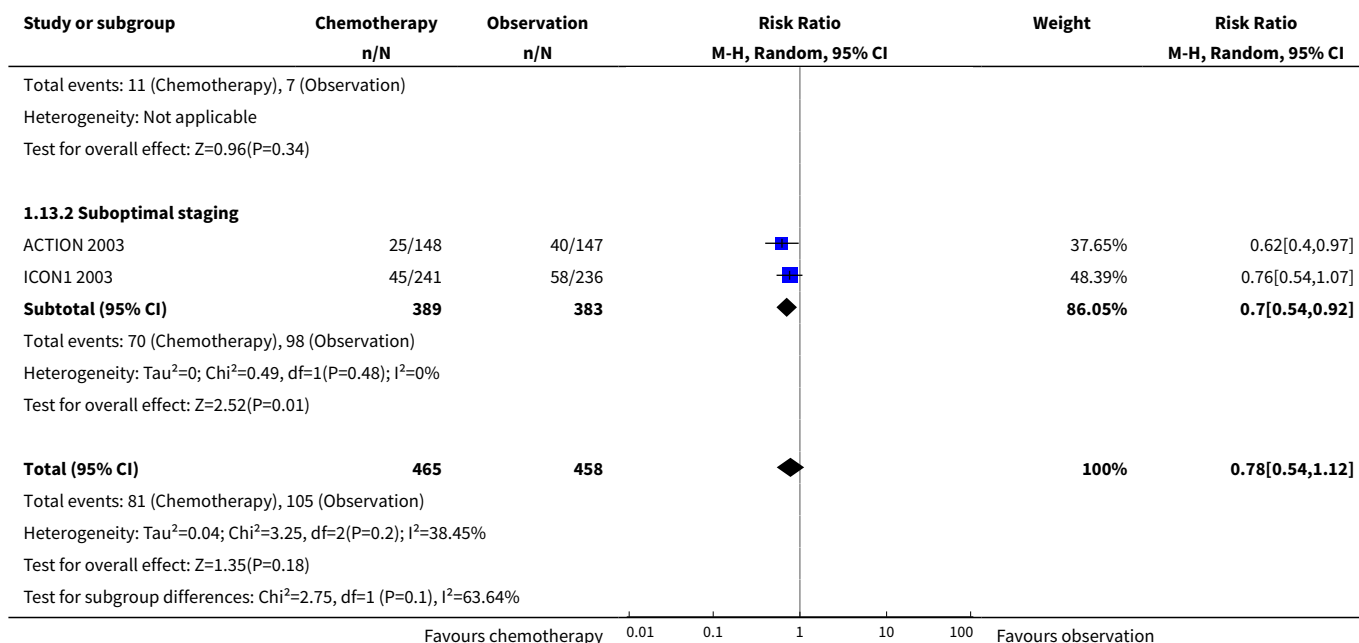


### Analysis 1.12. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 12 Subgroup analysis by staging: 10 yr DSS.

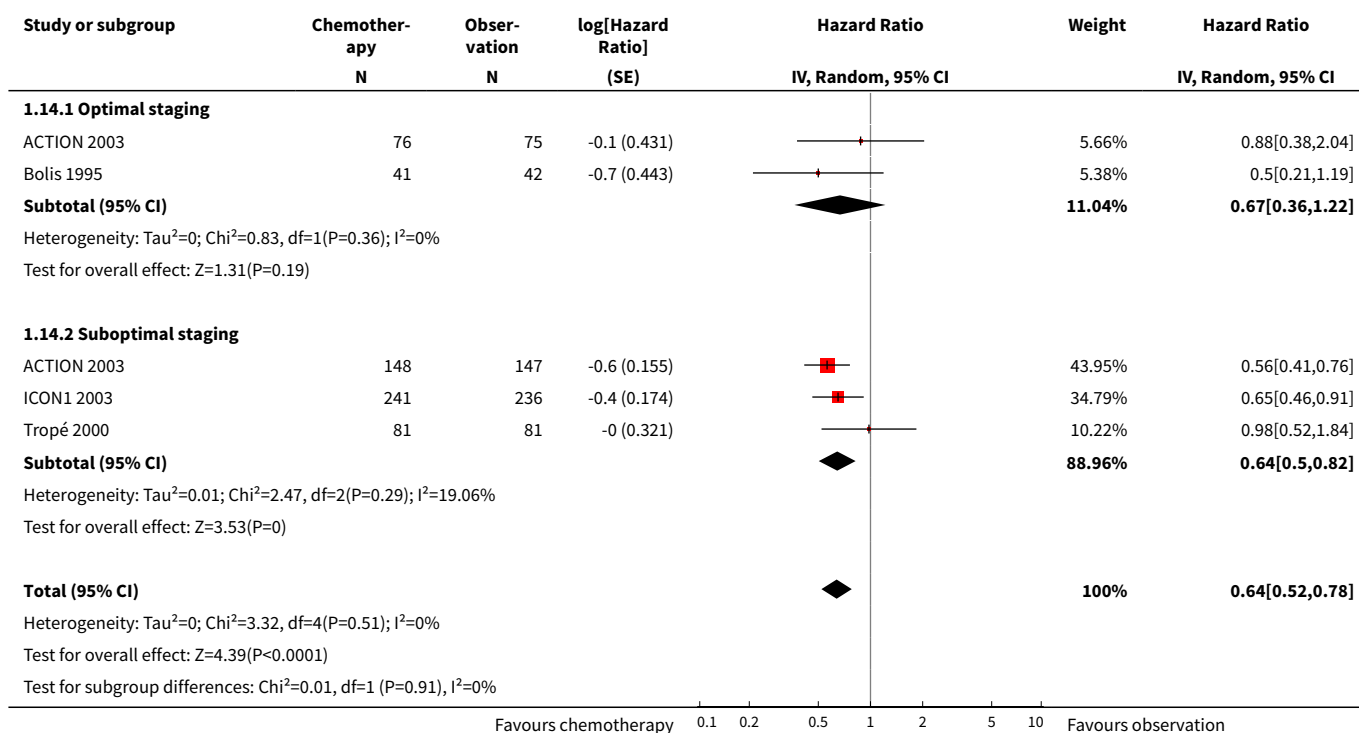


### Analysis 1.13. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 13 Subgroup analysis by staging: death from ovarian cancer (10 years).

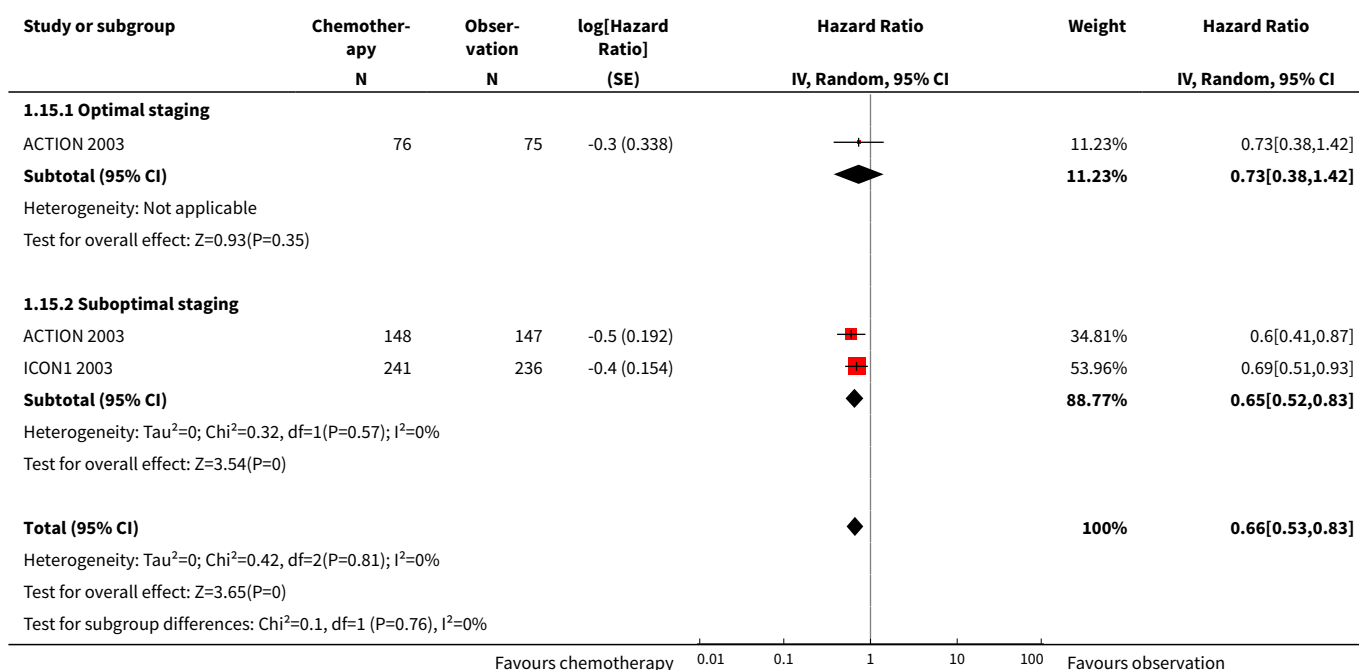




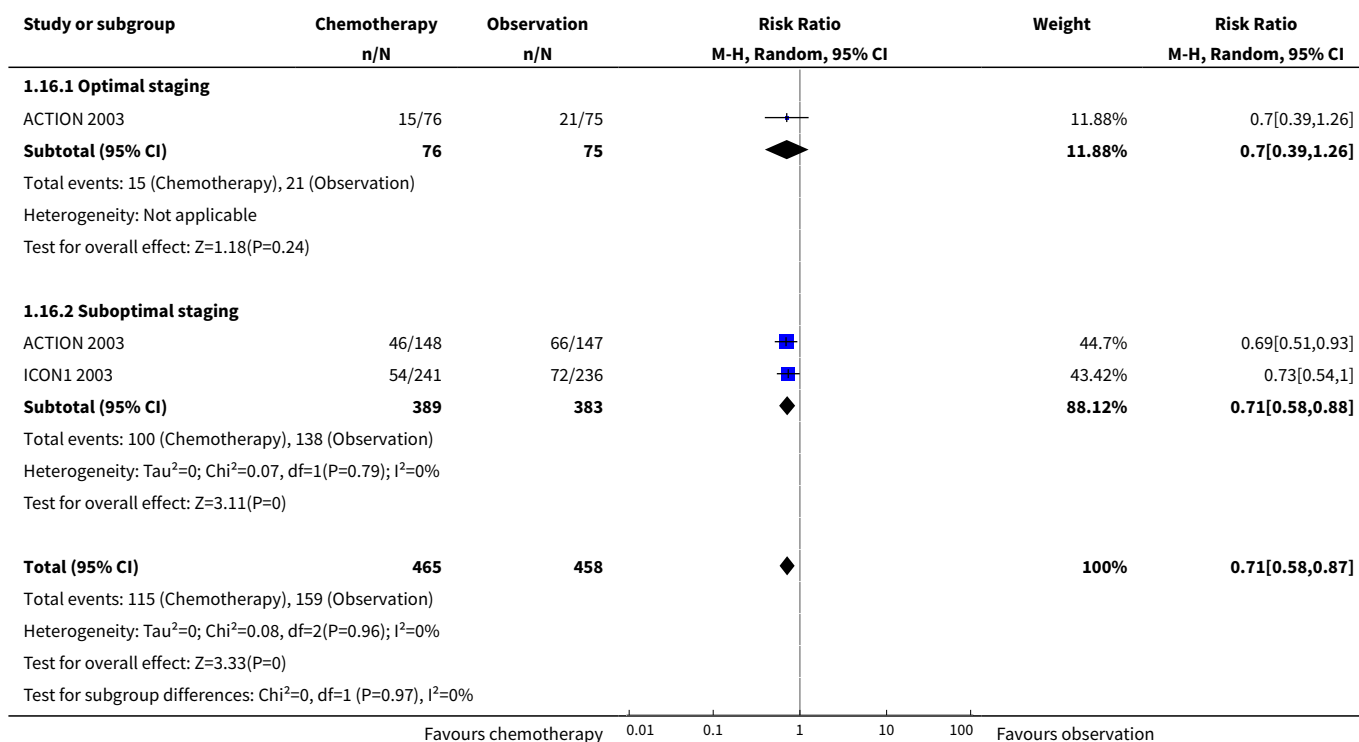
### Analysis 1.14. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 14 Subgroup analysis by staging: 5-yr PFS.



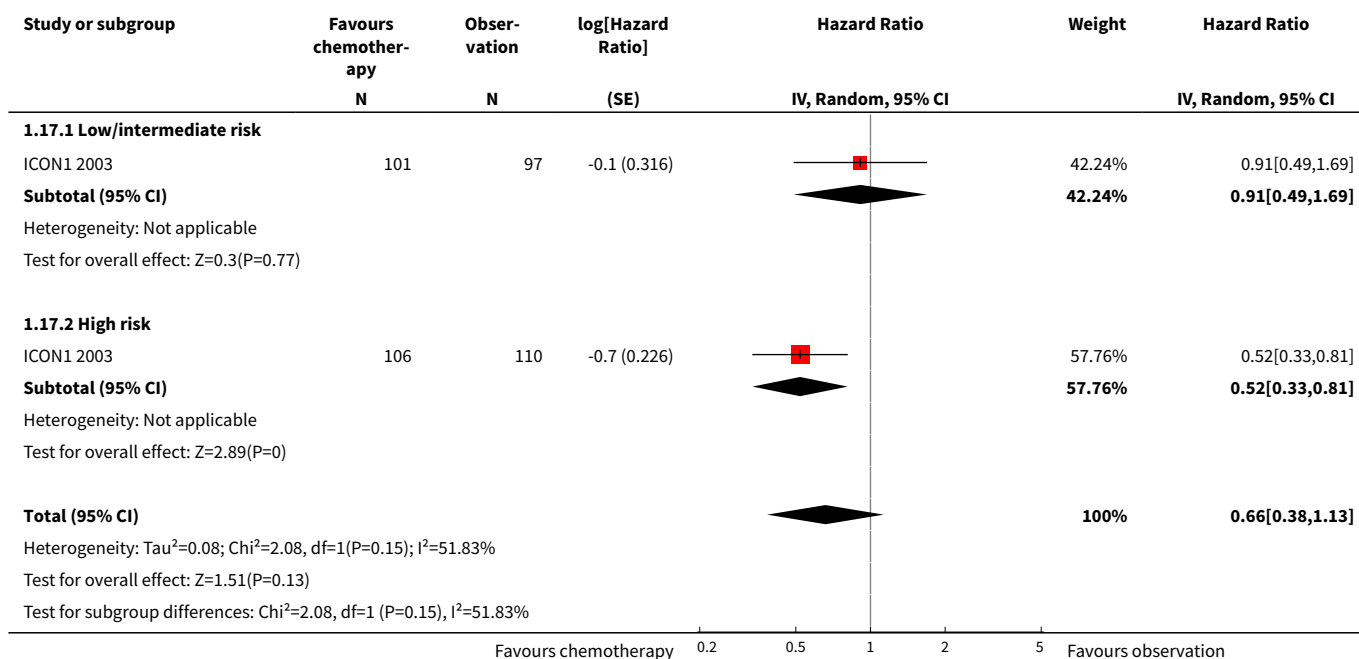
### Analysis 1.15. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 15 Subgroup analysis by staging: 10-yr PFS.



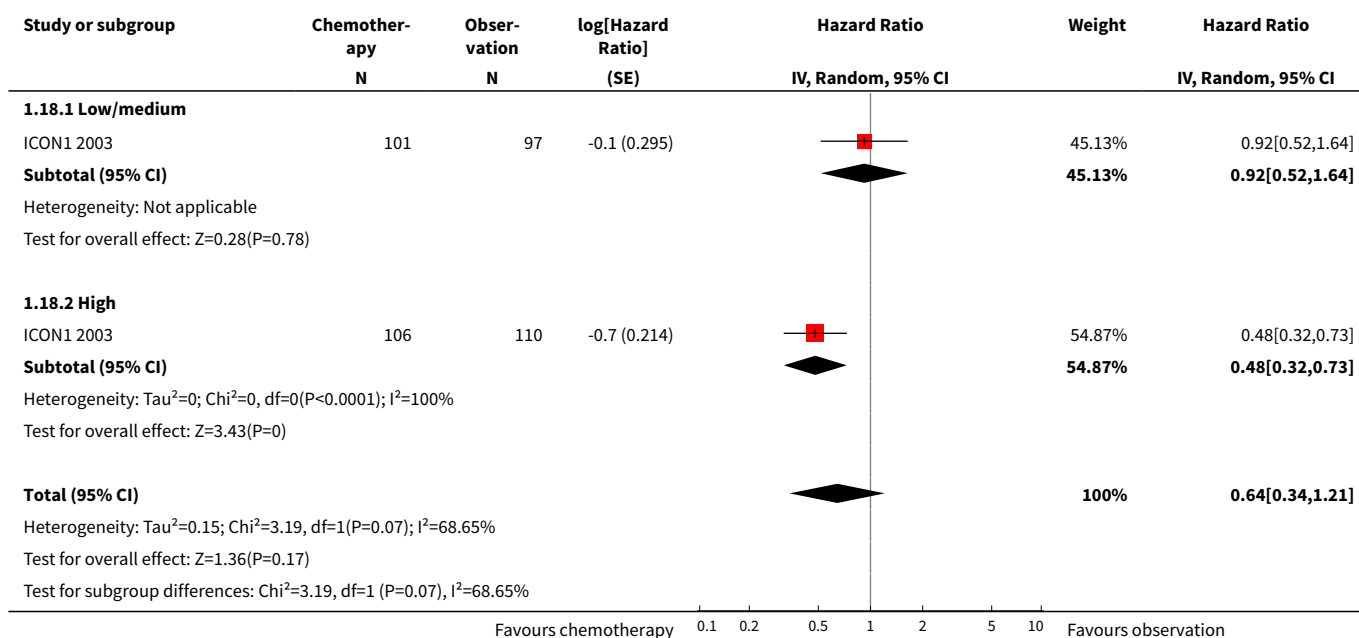
### Analysis 1.16. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 16 Subgroup analysis by staging: progression of ovarian cancer (10 years).



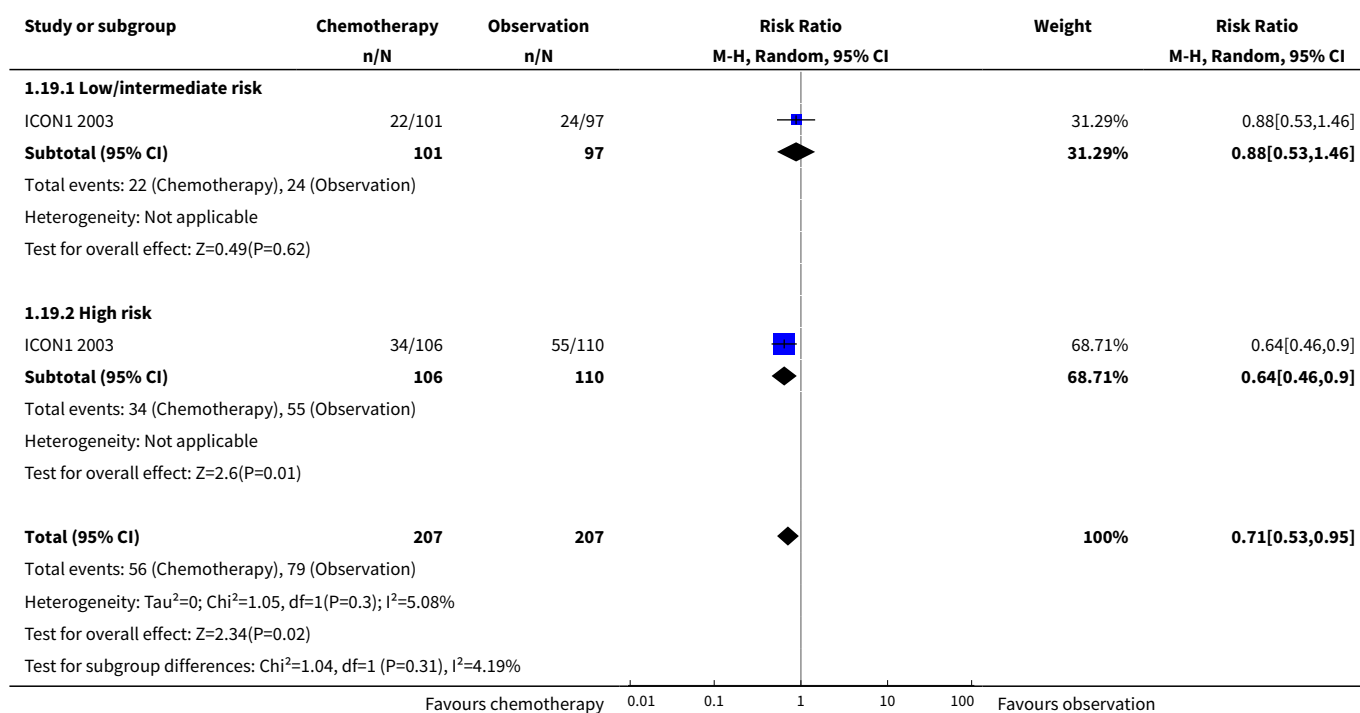
**Analysis 1.17. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 17 Subgroup analysis by risk: 10-yr OS.**



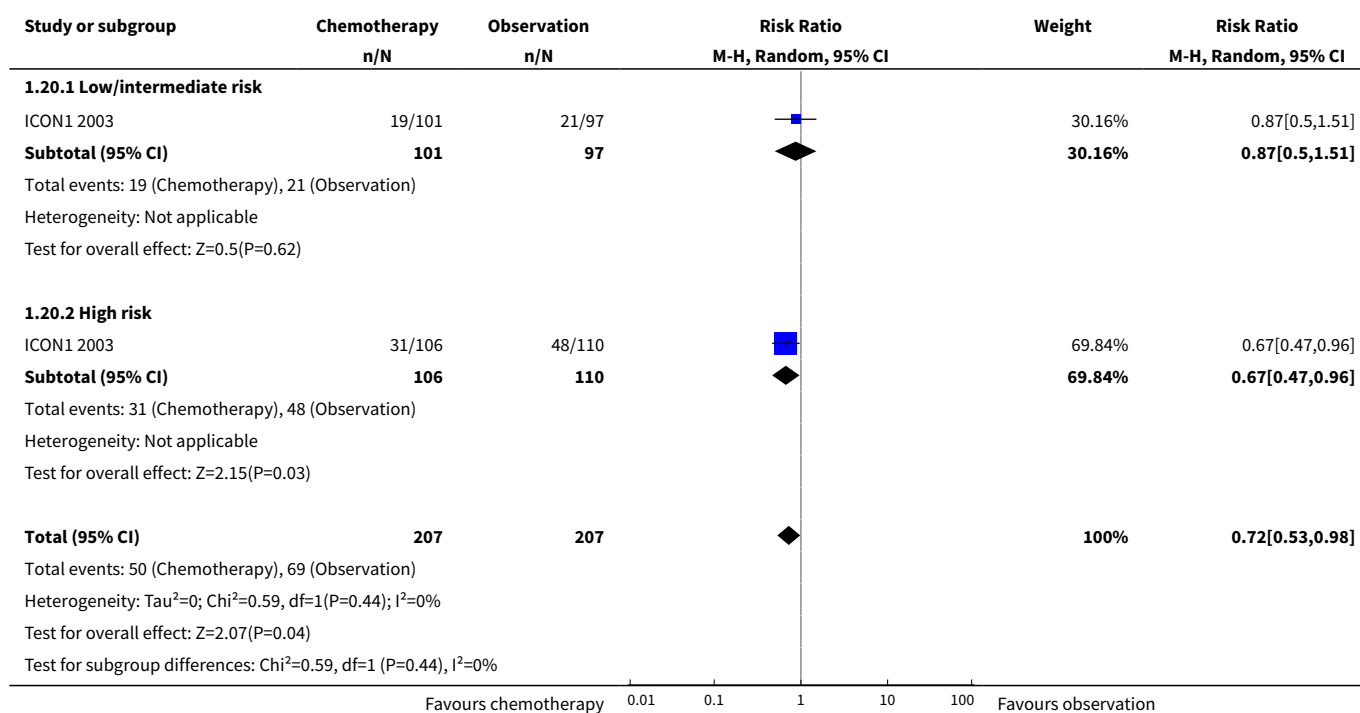
**Analysis 1.18. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 18 Subgroup analysis by risk: 10-yr PFS.**



### Analysis 1.19. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 19 Subgroup analysis by risk: progression at 10 yrs.



### Analysis 1.20. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 20 Subgroup analysis by risk: deaths by 10 yrs.



## ADDITIONAL TABLES

**Table 1. Staging of ovarian cancer**

Stage	Description
Ia	Disease confined to one ovary with no capsular involvement. Peritoneal washings/cytology negative.
Ib	Disease confined to both ovaries with no capsular involvement. Peritoneal washings/cytology negative.
Ic	Disease confined to the ovary/ovaries but ovarian capsulae involved or cyst rupture
IIa	Extension to uterus or fallopian tubes
IIb	Extension to other pelvic tissues
IIc	As for IIa or IIb but one or both ovaries have ruptured capsule or surface tumour; malignant ascites or positive peritoneal washings
IIIa	Histologically confirmed microscopic seeding of abdominal peritoneal surfaces and negative retroperitoneal lymph nodes
IIIb	Histologically confirmed implants of abdominal peritoneal surfaces less than 2 cm and negative retroperitoneal lymph nodes
IIIc	Histologically confirmed implants of abdominal peritoneal surfaces greater than 2 cm or positive retroperitoneal lymph nodes
IV	Distant metastases (including liver parenchyma/positive pleural fluid cytology)

**Table 2. RCTs of adjuvant treatment: description and quality assessment**

Study ID	Recruitment period	Staging	Comparison	Randomisation	Intention to treat	5-year follow-up
<a href="#">Smith 1975</a>	1969 to 1974	No	CT versus RT	Unspecified	No	Incomplete
<a href="#">Dembo 1979</a>	1971 to 1975	No	RT versus RT+CT	Stratified	No	Median 52 months
<a href="#">Hreshchyshyn 1980</a>	1971 to 1978	No	CT versus RT versus NA	Unspecified	No	No
<a href="#">Sigurdsson 1982</a>	1975 to 1978	No	NT versus CT, RT versus CT or (RT + CT)	Stratified, quasi-randomised	No	Yes
<a href="#">Sevelde 1987</a>	1980 to 1985	Yes complete in 60.5%	NA versus RT versus (RT + CT)	Unspecified	No	Median 42 months

**Table 2. RCTs of adjuvant treatment: description and quality assessment** (Continued)

Grönroos 1984	1976 to 1978	No	NA versus RT and NA versus CT	Randomised by birth month (quasi-randomisation)	No	3-year follow-up
Klaassen 1988	1975 to 1984	No	CT versus RT versus IPR	Central telephone	Yes	Median 8 years
Sell 1990	1981 to 1987	Complete	RT versus (RT + CT)	Block randomisation	Yes	4 years
Young 1990	1976	Complete	CT versus NA or IPR	Central, computer stratified	Yes	> 6 years
Young 2000		Complete	3 x CT versus 6 x CT	Central, computerised	Yes	> 6 years
Bell 2006						
Young 2003		Complete	CT versus IPR	Central, computerised	Yes	
Vergote 1992	1982 to 1988	Complete	CT versus IPR	Central, computer stratified	Yes	Median 62 months
Chiara 1994	1985 to 1989	Complete in 87%	CT versus RT	Central, computerised	Yes	
Bolis 1995	1983 to 1990	Complete	CT versus NA or IPR	Central, random generated numbers	Yes	Yes
Tropé 2000	1992 to 1997	Complete	CT versus NA	Central, computerised	Yes	Median 46 months
Kojs 2001	1990 to 1996	Complete	CT versus RT	Method not explicit	Yes	Yes
ICON1 2003	1990 to 2001	Incomplete	CT versus NA	Central computerised	Yes	Median 51 months
ACTION 2003	1990 to 2000	Complete	CT versus NA	Central, computerised	Yes	Median 66 months
Mannel 2011 (GOG 175)		Complete	CT + maintenance versus CT alone	Central, computerised	Yes	Yes

**Abbreviations:** **CT:** chemotherapy; **RT:** radiotherapy; **IPR:** intra-peritoneal radio-isotope therapy; **NA:** no additional treatment.



**Table 3. Trials of adjuvant chemotherapy versus no further treatment**

Study ID	Participants	Intervention	5-year survival rates	5-year survival/statistics	10-year survival rates	Adverse effects	Comments
<b>ICON1 2003</b>	447 FIGO I-III 93% FIGO stage 1	Immediate adjuvant platinum-based chemotherapy versus treatment on progression	OS 79% (adjuvant arm) versus 70% (no treatment)	HRs  OS: HR 0.66; 95% CI 0.45 to 0.97; P = 0.03	OS 73% (adjuvant arm) versus 64% (no treatment)	Not reported	Survival improvement with adjuvant therapy
<b>ACTION 2003</b>	448 FIGO Ia-Ib grade II-III FIGO Ic-IIa FIGO I-IIa clear cell	Immediate adjuvant platinum-based chemotherapy versus treatment on progression Cisplatin dose = 75 mg/m <sup>2</sup> Carboplatin dose = 350 mg/m <sup>2</sup>	OS 85% (adjuvant arm) versus 78% (no treatment)	HRs  OS: HR 0.69; 95% CI 0.44 to 1.08; P = 0.10 RFS: HR 0.63; 95% CI 0.43 to 0.92; P = 0.02	OS 77% (adjuvant arm) versus 70% (no treatment)	Not reported	Subgroup analysis showed that non-optimally staged patients in observation arm had significantly worse survival
<b>Tropé 2000</b>	162 high risk stage I 36% patients had low-volume residual disease	Carboplatin 6 cycles Q28/7 AUC = 7 versus chemo at progression	No difference between arms  DFS 70% versus 71%, OS 86% versus 85%	Log rank test  DFS P = 0.41 OS P = 0.43	NR	HRs  DFS: HR 0.98; 95% CI 0.52 to 1.83  DSS: HR 0.94; 95% CI 0.37 to 2.36	Not reported
<b>Young 1990</b>	48 treatment  44 observation	Melphalan versus no further treat	DFS 91% versus 98% OS 94% versus 98%	Log rank test DFS P = 0.41 OS P = 0.43	NR	Melphalan: 16% had severe myelosuppression. 26% had gastrointestinal side effects. One death: myeloproliferative disorder aplastic anaemia 6 years after completing treatment.	Trial under powered to show any real differences
<b>Bolis 1995</b>	85 FIGO (1976) I A-I B Grade 2 and 3	Cisplatin 50 mg/m <sup>2</sup> × 6 cycles Q28/7 versus no further treatment	DFS 83% versus 64% OS 88% versus 82%	HRs  DFS: HR 0.50; 95% CI 0.21 to 1.19; P = 0.17  OS: HR 1.20; 95% CI 0.46 to 3.1; P = 0.71	NR	Nausea and vomiting in more than two-thirds of patients in cisplatin arm. Severe in less than 10%. Leucopenia 14%; thrombocytopenia 8%; neurological toxicity 6%; renal toxicity 7%	There were patients with residual disease in both arms

**Abbreviations; CI:** confidence interval; **DFS:** disease-free survival; **HR:** hazard ratio; **OS:** overall survival; **RFS:** recurrence-free survival; **AUC:** area under the concentration curve; **NR:** not reported.

**Table 4. 10-year survival rates of adjuvant chemotherapy versus observation according to risk**

10 year survival outcomes for women with early stage ovarian cancer	Adjuvant chemotherapy		Observation		P value
	n/N	%	n/N	%	
Risk of death (all early stage disease) <sup>1</sup>	118/465	25%	152/460	33%	0.009
Risk of progression or death (all early stage disease) <sup>1</sup>	132/465	28%	181/460	39%	0.0005
Risk of death (low/intermediate risk disease) <sup>2</sup>	19/101	19%	21/97	22%	NS
Risk of progression or death (low/intermediate risk disease) <sup>2</sup>	22/101	22%	24/97	25%	NS
Risk of death (high risk disease) <sup>2</sup>	31/106	29%	48/110	44%	0.03
Risk of progression or death (high risk disease) <sup>2</sup>	34/106	32%	55/110	50%	0.009

<sup>1</sup>Based on [ACTION 2003](#) and [ICON1 2003](#) 10-year follow-up data.

<sup>2</sup>Based on [ICON1 2003](#) 10-year follow-up subgroup data.

**Abbreviations:** NS: not statistically significant;

## APPENDICES

### Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Ovarian Neoplasms explode all trees
- #2 ovar\* near/5 (cancer\* or tumor\* or tumour\* or neoplas\* or carcinoma\* or malignan\*)
- #3 (#1 OR #2)
- #4 Any MeSH descriptor with qualifier: DT
- #5 MeSH descriptor Antineoplastic Agents explode all trees
- #6 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols, this term only
- #7 chemotherap\*
- #8 (#4 OR #5 OR #6 OR #7)
- #9 Any MeSH descriptor with qualifier: SU
- #10 MeSH descriptor Surgical Procedures, Operative explode all trees
- #11 surg\* or procedure\* or intervention\*
- #12 (#9 OR #10 OR #11)
- #13 (#8 AND #12)
- #14 MeSH descriptor Chemotherapy, Adjuvant explode all trees
- #15 chemotherap\* and adjuvant
- #16 (#14 OR #15)
- #17 (#13 OR #16)
- #18 (#3 AND #17)

This search strategy yielded the following results, including duplicates: CENTRAL = 485 references.

### Appendix 2. MEDLINE search strategy 2011

The 2011 MEDLINE (Ovid) search strategy (1948 to September 2011) was as follows:

1. exp Ovarian Neoplasms/
2. (ovar\* adj5 (cancer\* or tumor\* or tumour\* or neoplas\* or carcinoma\* or malignan\*)).mp.
3. 1 or 2

4. drug therapy.fs.
5. exp Antineoplastic Agents/
6. Antineoplastic Combined Chemotherapy Protocols/
7. chemotherap\*.mp.
8. 4 or 5 or 6 or 7
9. surgery.fs.
- 10.exp Surgical Procedures, Operative/
- 11.(surg\* or procedure\* or intervention\*).mp.
- 12.9 or 10 or 11
- 13.8 and 12
- 14.Chemotherapy, Adjuvant/
- 15.(chemotherap\* and adjuvant).mp.
- 16.14 or 15
- 17.13 or 16
- 18.3 and 17
- 19.randomized controlled trial.pt.
- 20.controlled clinical trial.pt.
- 21.randomized.ab.
- 22.placebo.ab.
- 23.clinical trials as topic.sh.
- 24.randomly.ab.
- 25.trial.ti.
- 26.19 or 20 or 21 or 22 or 23 or 24 or 25
- 27.18 and 26

key:

- mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier
- pt = publication type
- ab = abstract
- sh = subject heading

This search strategy yielded the following results, including duplicates: total MEDLINE = 997 references.

### Appendix 3. EMBASE search strategy

- 1 exp ovary tumor/
- 2 (ovar\* adj5 (cancer\* or tumor\* or tumour\* or malignan\* or carcinoma\* or neoplasm\*)).mp.
- 3 1 or 2
- 4 exp chemotherapy/
- 5 exp antineoplastic agent/
- 6 chemotherap\*.mp.
- 7 4 or 5 or 6
- 8 exp gynecologic surgery/
- 9 (surgery or surgical\* or procedure\* or intervention\*).mp.
- 10 8 or 9
- 11 7 and 10
- 12 adjuvant chemotherapy/
- 13 (adjuvant adj5 chemotherap\*).mp.
- 14 12 or 13
- 15 11 or 14
- 16 3 and 15
- 17 crossover procedure/
- 18 randomized controlled trial/
- 19 single blind procedure/
- 20 random\*.mp.
- 21 factorial\*.mp.

22 (crossover\* or cross over\* or cross-over).mp.  
 23 placebo\*.mp.  
 24 (doubl\* adj blind\*).mp.  
 25 (singl\* adj blind\*).mp.  
 26 assign\*.mp.  
 27 allocat\*.mp.  
 28 volunteer\*.mp.  
 29 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28  
 30 16 and 29

key:

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

This search strategy yielded the following results, including duplicates: EMBASE = 1630 references.

## Appendix 4. 'Risk of bias' assessment

We evaluated risk of bias using the following criteria:

### 1. Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it had produced comparable groups. We assessed the method as:

- low risk of bias (any truly random process, e.g. a computer-generated random sequence or a table of random numbers);
- high risk of bias (any non-random process, e.g. quasi-randomised: date of birth, clinic ID number or surname);
- unclear, e.g. not reported.

### 2. Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as:

- low risk (e.g. by telephone randomisation, or use of consecutively numbered, sealed, opaque envelopes);
- high risk (e.g. open random number lists or quasi-randomisation such as alternate days, odd/even date of birth, or hospital number, unsealed or non-opaque envelopes);
- unclear, e.g. not reported.

### 3. Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes. We assessed methods used to blind outcome assessment as:

- low risk;
- high risk;
- unclear.

### 4. Loss to follow-up/incomplete outcome data (checking for possible attrition bias)

We recorded the proportion of participants whose outcomes were not reported at the end of the study; we noted if loss to follow-up was not reported. We assessed loss to follow-up as:

- low risk, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
- high risk, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms;
- unclear, if loss to follow-up was not reported.

### 5. Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias. We assessed the methods as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review had been reported and analyses were by intention-to-treat (ITT));

- high risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported; analyses not by ITT);
- unclear risk of bias.

## 6. Other bias (checking for bias due to problems not covered by 1 to 5 above)

We described for each included study any important concerns we had about other possible sources of bias, e.g. an imbalance in baseline/prognostic factors.

## WHAT'S NEW

Date	Event	Description
21 September 2016	Amended	Contact details updated.

## HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 1, 2009

Date	Event	Description
4 September 2015	New citation required but conclusions have not changed	We added 10-year follow-up data for the ICON I trial from <a href="#">Collinson 2014</a> .
1 April 2015	Amended	We updated the review authors' contact details.
24 March 2015	New search has been performed	We conducted a literature search update.
11 February 2015	Amended	We updated review authors' contact details.
27 March 2014	Amended	We updated review authors' contact details.
6 February 2012	New citation required but conclusions have not changed	<p>We designed a new literature search strategy and performed a literature search up to 06 February 2012 (<a href="#">Appendix 2</a>).</p> <p>The updated literature search identified 11 additional citations (16 September 2011), including nine reports/conference abstracts relating to five previously classified studies. We added two reports to the 'Studies awaiting classification' section.</p> <p>Of the 11 citations identified by the updated search, we excluded two studies and added nine citations to previously classified studies. We have added long-term ACTION data to the '<a href="#">Data and analyses</a>' section.</p>
6 February 2012	New search has been performed	A new author Tess Lawrie joined the review team.
18 May 2011	Amended	We performed a literature search update and amended the Methods section.
2 March 2009	New citation required but conclusions have not changed	We performed further editing to the review.
5 June 2008	Amended	We converted to a new review format.

## CONTRIBUTIONS OF AUTHORS

BWR wrote the protocol, conducted the original literature search, identified the studies for inclusion, abstracted data, and wrote the original review ([Winter-Roach 2009](#)) together with the review authors. HK edited and provided advice regarding the Cochrane protocol, helped in the selection of studies and data abstraction, and contributed to the original ([Winter-Roach 2009](#)) and updated review ([Winter-Roach 2012](#)). TL abstracted the long-term follow-up data and updated the statistical analyses and text of the review. Pauline Heus assisted with the literature search and study selection for this review update. All review authors read and approved the final version.

## DECLARATIONS OF INTEREST

BWR has no known conflicts of interest.

TL has no known conflicts of interest.

PH has no known conflicts of interest.

HK has no known conflicts of interest.

## SOURCES OF SUPPORT

### Internal sources

- Cochrane through the Department of Health, UK.

### External sources

- None, Other.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol we did not specify subgrouping data by risk. After publication of an abstract reporting the effect of adjuvant chemotherapy compared to no adjuvant chemotherapy in subgroups of high risk and intermediate/low risk women in the [ICON1 2003](#) trial, we decided to present these subgroup data in the review. We have discussed this deviation from the protocol in the 'Risk of reviewer bias' section of the [Discussion](#).

We have updated the [Methods](#) section of this review since the publication of the protocol, to include updated methods for assessing risk of bias, missing data, and assessing heterogeneity.

In addition to time-to-event survival meta-analysis, we performed meta-analysis using dichotomous data to inform illustrative comparative risks.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antineoplastic Agents [\*therapeutic use]; Carboplatin [therapeutic use]; Chemotherapy, Adjuvant [methods]; Cisplatin [therapeutic use]; Disease-Free Survival; Early Detection of Cancer; Melphalan [therapeutic use]; Neoplasm Staging; Ovarian Neoplasms [\*drug therapy] [pathology] [surgery]; Randomized Controlled Trials as Topic

### MeSH check words

Female; Humans